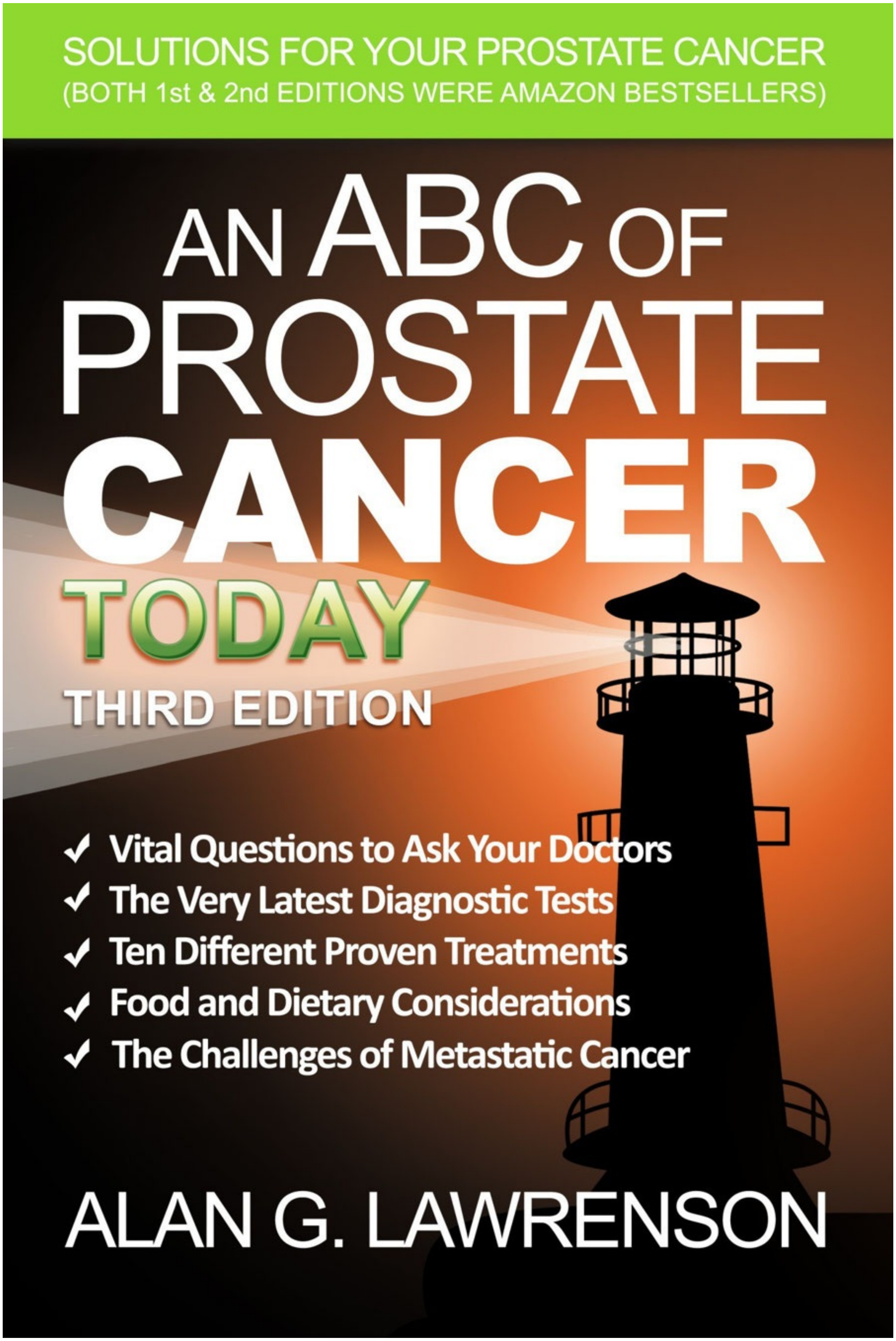


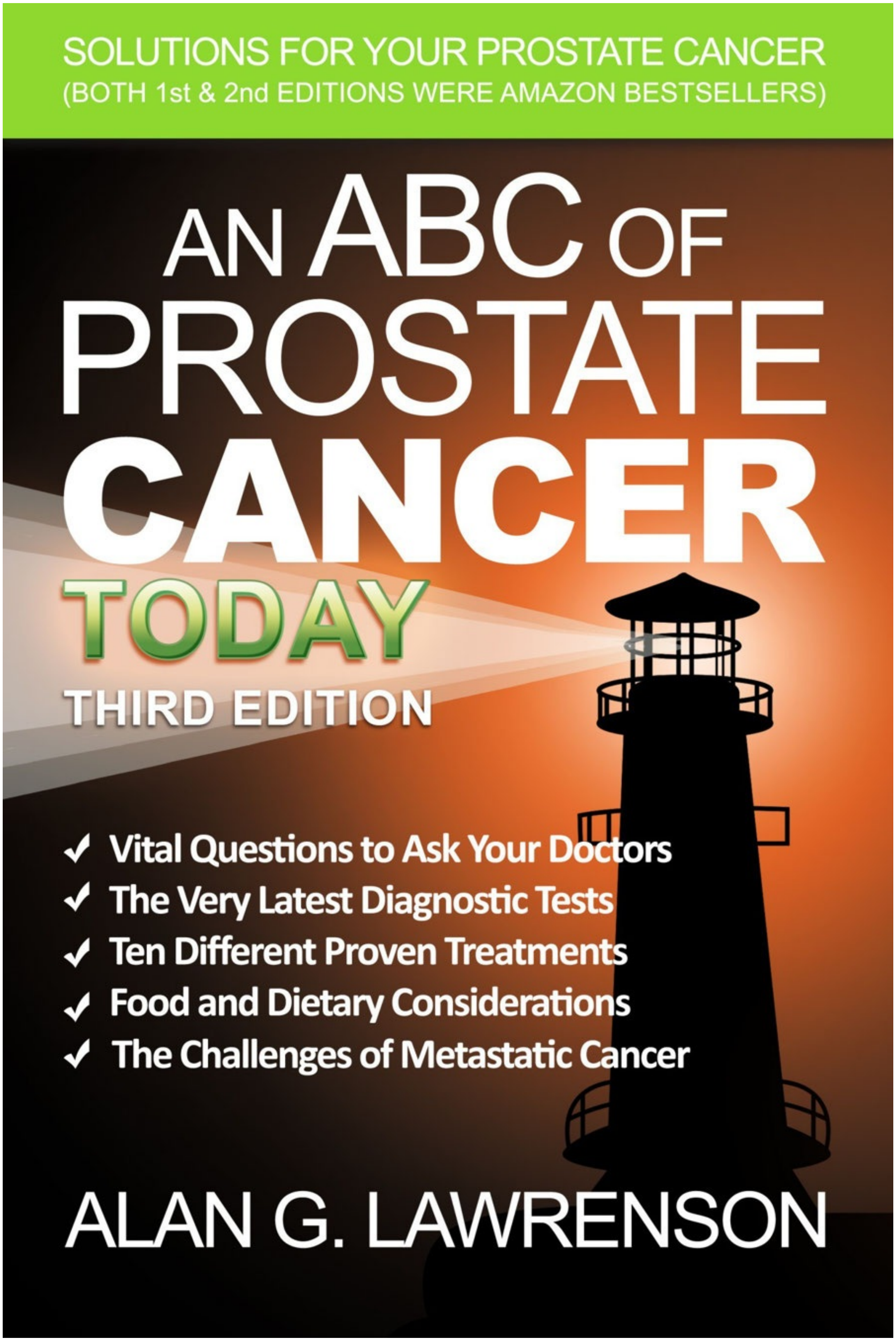
SOLUTIONS FOR YOUR PROSTATE CANCER
(BOTH 1st & 2nd EDITIONS WERE AMAZON BESTSELLERS)

AN ABC OF PROSTATE CANCER TODAY

THIRD EDITION

- ✓ Vital Questions to Ask Your Doctors
- ✓ The Very Latest Diagnostic Tests
- ✓ Ten Different Proven Treatments
- ✓ Food and Dietary Considerations
- ✓ The Challenges of Metastatic Cancer

ALAN G. LAWRENSON



SOLUTIONS FOR YOUR PROSTATE CANCER
(BOTH 1st & 2nd EDITIONS WERE AMAZON BESTSELLERS)

AN ABC OF PROSTATE CANCER TODAY

THIRD EDITION

- ✓ Vital Questions to Ask Your Doctors
- ✓ The Very Latest Diagnostic Tests
- ✓ Ten Different Proven Treatments
- ✓ Food and Dietary Considerations
- ✓ The Challenges of Metastatic Cancer

ALAN G. LAWRENSON

AN ABC OF PROSTATE CANCER TODAY

Third Edition

Solutions For Your Prostate Cancer

Alan G. Lawrenson

Third Edition – Copyright © 2019 Alan G. Lawrenson

Published by Alan G. Lawrenson, Sydney, NSW, Australia

Design and Layout by Alan G. Lawrenson

ISBN: 978-0-9943197-5-3

Disclaimer: Every care has been taken in preparing this book to present information fully, accurately and correctly. The author takes NO RESPONSIBILITY for any information that might not be accurate and correct, fully covered or excluded, either intentionally or in error. Furthermore, the information in this book is provided under the understanding that the author is not rendering medical advice. The sole purpose of this book is to assist the reader to ask informed questions of their qualified healthcare professionals. IT IS IMPERATIVE THAT ALL PERSONS READING THIS BOOK, SHOULD SEEK THE SERVICES OF EXPERIENCED AND APPROPRIATE MEDICAL PROFESSIONALS TO DIAGNOSE AND/OR TREAT ANY CONDITION, DISEASE OR MALADY THAT THEY MAY OR MAY NOT HAVE. The author of this book is not a medical doctor, and the reader is advised that any information or opinions expressed or implied in this book are those of a layman and should not be acted upon without the consent of a qualified medical professional. The author is expressly not liable for any damages or negative consequences that might follow from any treatment, actions or procedures undertaken by any person or persons reading or following the contents, information or opinions within this book, including the research papers referred to in the book.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

DEDICATION

This book is dedicated to two people:

Dudley C. R. Clear

He was my English master from 1958 to 1962 at the Grey High School in Port Elizabeth, South Africa. He instilled in me a great liking of the English language; how it ought to be written and spoken. His English skills rubbed off on me to a substantial extent. This has allowed me to progress through life with a good command of the spoken and written word. He was more than a teacher: he was a Master of his craft. His tutoring and guidance instilled in me the desire to be an author one day. It has taken 52 years to achieve this goal.

Brian Stanley Lawrenson

My dearest brother died, aged 79, on the 22nd January 2020 from prostate cancer. He contribution to the north-western Sydney community, over the 20 years that he suffered from prostate cancer, was immense. He became President of his Rotary Club in 2003. In 2008 he served as the Charter President of the new Rotary Club of Breakfast Point. He was the founding President of two new Probus Clubs and went on to author 70 travel eBooks. (He and his wife Jill travelled to more than 70 countries over 50 years together). He became a sort-after destination speaker on the world’s premier cruise lines.

Above all, he fought his disease with great courage, maintaining his great sense of humour, dedication to causes that interested him, and continued his ongoing support of my efforts to assist families touched by prostate cancer.

A FINAL MESSAGE:

ALL MEN FROM THE AGE OF 40 SHOULD START UNDERGOING REGULAR PSA AND DRE TESTING

CONTENTS

PART 1: MY INITIAL DIAGNOSIS

Chapter 1. I am diagnosed with Prostate Cancer

Chapter 2. What is Prostate Cancer

Chapter 3. How is Prostate Cancer detected?

Chapter 4. Imaging

PART 2: TREATMENT OPTIONS

Chapter 5. Introductory Comments on Treatment Options

Chapter 6. Active Surveillance or Watchful Waiting

Chapter 7. Surgery

Chapter 8. Radiation

8.1 External Beam Radiation Therapy (EBRT)

8.2 3-D CRT, IMRT, IGRT and Tomography

8.3 Stereotactic Body Radiotherapy (SBRT)

8.4 Proton Beam Therapy

8.5 Low Dose Brachytherapy (Seeds)

8.6 High Dose Brachytherapy

8.7 Radioactive Ligand Therapy (^{177}Lu PSMA Therapy)

Chapter 9. Hyperthermia

Chapter 10. Cryosurgery

Chapter 11. High Intensity Focussed Ultrasound (HIFU)

Chapter 12. Focal Laser Ablation

Chapter 13. Hormone Therapy

Chapter 14. Chemotherapy and Immunotherapy

Chapter 15. mCRPC, Genetics and Precision Medicine

Chapter 16. PARP and Other Inhibitor

Chapter 17. Sexual Function and Incontinence

Chapter 18. The Plan to Successfully Fight Off Cancer

Chapter 19. Complementary Therapies

Chapter 20. Diet and Nutrition

Chapter 21. Aternative Therapies

Chapter 22. Future Developments

Chapter 23. The Role of Support Groups

PART 3: MY PROSTATE CANCER EXPERIENCE

Chapter 24. My Prostate Cancer: Ongoing Research

Chapter 25. Was HIFU the Answer?

Chapter 26. A Third Urologist Enters the Picture

Chapter 27. Proton Beam Therapy Re-Visited

Chapter 28. Enter the Radiation Oncologist

Chapter 29. Enter the Case for Hyperthermia

Chapter 30. How Do You Get to a Final Treatment Decision?

Chapter 31. The Decision: Proton Beam Therapy in Korea

Chapter 32. The Pre-Treatment Program in Korea

Chapter 33. My Treatment Begins

Chapter 34. The Post Treatment Period

Chapter 35. Would I Make the Same Decision Again?

Appendix 1. Glossary

Appendix 2. Abbreviations

Appendix 3. Resource Listings

Appendix 4. Reference Listings

Appendix 5. Proton Beam Therapy Centres

Appendix 6. Acknowledgements

INTRODUCTION

What this Book is and What it is Not

This book is about a number of things.

Firstly, it tells the story of me being diagnosed with intermediate stage prostate cancer. This level of prostate cancer needs active medical intervention. Unnecessary delays could result in the cancer developing into the advanced localised stage or worse, over time, into life threatening metastatic prostate cancer.

Secondly, it examines the ten to twelve treatment options that are available to prostate cancer sufferers today, plus subsets of some of these treatments, e.g. there are ten forms of radiation therapy discussed in this book. It includes details of the most common treatments and others that are a little less so. With the possible exclusion of complementary and alternative medicine, all these treatments are being practised daily by medical professionals around the world. All have been subjected to significant research and scrutiny and almost all have been the subject of successful randomised clinical trials. In the two chapters on complementary and alternative medicine, I present information on a number of relatively new treatments, which are still undergoing clinical trials or are still to do so and as a result have not yet reached the medical main stream.

All information in this book has been based on my own experiences or from my very extensive search of the information on prostate cancer that is in the public domain. This has included books on prostate cancer, web sites of hospitals, universities and research institutes, government bodies such as the US National

Institute of Health, not-for-profit bodies such as the Australian Cancer Council, proceedings from learned societies, other web sites, testimony by fellow prostate cancer suffers, input from medical practitioners (both physicians and surgeons) and other reliable sources.

Since publishing the first edition of this book, which was titled ‘An ABC of Prostate Cancer in 2015’, I have been fortunate to present ‘my story’ at many prostate cancer support groups around Australia. I have met many gravely ill men, who are still searching for a solution to their metastatic cancer. August 2016 saw the introduction of an updated book titled ‘An ABC of Prostate Cancer Today.’ This edition of the book included new material that had relevance to these sufferers and their families. Over the past two years, we have seen considerable progress in the research into prostate cancer and in its clinical treatment. In a book that is read by thousands of prostate cancer sufferers, it is essential that the very latest developments in the field are presented to ‘assist’ sufferers and the families to make informed choices. Thus, the introduction of ‘An ABC of Prostate Cancer Today – Third Edition.’ As an aside, I am appalled that prostate cancer books written five or even fifteen years ago, are still available for sale. Human biology hasn’t changed, but diagnostics, imaging and medical treatments have improved many-fold.

Thirdly, it outlines the process I went through, to find the best treatment option to suit my particular circumstances. It also details the actual treatment process that I underwent. Finally, I look back at my treatment and whether I would make the same selection again after reviewing the outcomes achieved and the new information gleaned in the process of researching and writing this book.

Hopefully you will find this book an interesting and informative read. I also hope that it will give prostate cancer sufferers and their families, a wider general overview of the processes and procedures that might be available to them and prepare them, more fully, to effectively engage with their medical team.

What this book is NOT, is medical advice. I am NOT a doctor, nor have I been trained in medicine. Thus, it is imperative that all prostate cancer sufferers, their families and supporters, who read this book, seek appropriate medical advice from medical professionals.

Every patient has differing characteristics and circumstances that can only be assessed by competent medical professionals. Reading this book may be helpful in at least providing useful background information that might assist in the critically important patient/doctor dialogue, which is so necessary at every stage of the journey to beat the cancer. The questions listed in the book under various treatment options might be appropriate for some patients, but not for others. Take from the book what you will, but beyond all else, take heed of what your medical team are recommending and act on it.

All care has been taken in preparing this book to present information fully, accurately and correctly. I take NO RESPONSIBILITY for any information that might not be accurate and correct, fully covered or excluded, either intentionally or in error.

Things are moving very quickly in the prostate cancer treatment field. What was good advice yesterday, might not be so tomorrow. New information becomes available every day! I have had difficulty in deciding what new or relatively new information to include. Tomorrow might see the announcement of a significant breakthrough. Thus, I have drawn a line under what is to be included in this edition. The first and second editions of this book have reached bestseller status, which has encouraged me to present this new edition with many new snippets of the latest information on the disease.

What background or training equipped me to write what is partially a technical review of treatments that are available for prostate cancer?

After being tertiary educated in the physical sciences, I worked in the commercial side of science for 46 years before retiring in 2006. Much of the last decade until 2006, was spent as the chief executive of an organisation called Science Industry Australia Inc. The SIA, as it was often referred to, was (and still is) a peak industry body, whose core purpose was/is the growth of the science industry in Australia. I was extensively involved with the Australian Federal Government in the establishment and implementation of the Science Industry Action Agenda and the Medical Devices Action Agenda. These Action Agendas were the mechanism used by the then John Howard’s Coalition Government, to grow the commercialisation output of scientific and medical research institutes, universities and hospitals into products or services that could be marketed by these two industries, locally and internationally. I also spent 10 years attending the Board of the peak umbrella body of scientific and medical research professional societies from 1995 to 2006. Over a 25-year period, I had the privilege to attend more than 100 scientific and medical conferences in Australia, the USA, the UK, Japan, Singapore, Germany and South Africa. These activities have seen me develop an ability to translate technical research findings into more simplified documents that could be understood by non-scientific or non-medical personnel.

This new edition of the book was written for four main reasons. Firstly, I aimed to provide what I believe to be a comprehensive review of the ‘state of play’ in the treatment of prostate cancer. Secondly, I hope to perhaps assist newly-diagnosed patients to pause and to take a step back, whilst they are in what I call ‘Cancer Anxiety Factor’ mode. It is very difficult to consider the treatment options offered them by their medical specialists or other alternatives, when faced with the psychological pressure to immediately rid oneself of the cancer. One needs time to weigh up the advantages and disadvantages of the various options available. Thirdly, I feel that proton beam therapy (and some of the lesser known treatment options) presents men with perhaps greater certainty of outcome compared to surgery, x-ray radiation or brachytherapy. Fourthly, over the last few years, I have become more convinced than ever, that diet, nutrition and exercise, play an important role in fighting cancer and keeping it at bay in healthy individuals.

The sub-title of this 3rd edition has been changed from ‘My Journey over 4 Continents to find the Best Cure’ to ‘Solutions for Your Prostate Cancer.’ Many doctors will tell you that there is no such thing as a ‘cure’ for cancer, but there is only ‘remission’ from the cancer. I don’t disagree with this point of view, but initially found it easier to use the word ‘cure’ in the title. Now the book is about discovering relevant information that sufferers can discuss with their medical teams. Finally, after much consideration, I decided not to identify any of the doctors in this book by name, other than Dr Cho Kwan-Ho, who was responsible for my treatment at the National Cancer Centre’s proton beam facility in Korea. I can say that all the doctors that I came across in my journey, were highly competent and had my best interests at heart. My use of an initial to identify them, should not suggest anything to the reader or indeed the doctor in question. (should they read this book)!

One last technical note. Most of the images in this book were sourced as full colour images that might not be as clear when presented in black and white as they are in this book. The colour images will be viewable in colour on the book’s web site at www.anabcofprostatecancer.com.au.

PART 1: MY INITIAL DIAGNOSIS

Chapter 1.

I am Diagnosed with Prostate Cancer

It was mid-April 2012. A few days following my biopsy to determine whether or not the acceleration of my PSA (Prostate Specific Antigen) reading was due to prostate cancer, I walked into Dr P’s rooms to discuss the biopsy results without any real foreboding. After all, my wife and I were about to jet out of Sydney (Australia) for a four-week holiday in South Africa. We had emigrated from there in 1979.

As my late father had prostate cancer for the last 25 years of his life and my late brother also had prostate cancer for the last 20 years, I was a little preconditioned to receiving bad news. Researchers in the 70’s had established a significant hereditary link between male family members. In my case, the chances of getting prostate cancer were suggested to me as being as high as 80%. However, an authoritative study suggests the likelihood is actually about 30%.[1]

Dr P, whom I knew as a fellow golfer, said as we sat down; “Alan, you have prostate cancer. The pathologist found that 9 of the 24 rods taken during the biopsy, were cancerous to a lesser or greater extent.” I felt a little stunned to say the least. Where was this news likely to take me?

The rest of the fifteen-minute consultation became a bit of a blur. The doctor explained that I had Type 1c prostate cancer with a Gleason score of 3 + 4 = 7. This is an intermediate grade cancer that was likely to grow more rapidly than one with a lower Gleason score of 6 or below, but slower than one with a score of 8 to 10, which are the most aggressive grades. Type 1 and Type 2 prostate cancers are considered to be still confined to the ‘box’ and are likely not to have spread to the seminal glands or other parts of the body.

Dr P then went on to discuss treatment options. These included a prostatectomy or radiation therapy. Of course, not much sank in, as I was in a state of mild shock. He gave me a copy of the Australian Cancer Council’s comprehensive 128-page book on prostate cancer titled ‘Localised Prostate Cancer – A guide for men and their families.’ (Unfortunately, this book is no longer available in hard copy or online).

I walked out of the doctor’s rooms after making an appointment to see him in mid-June 2012 after my return from South Africa. (I returned from South Africa a day or two after Dr P went overseas for a month, thus delaying the next appointment). This delay in considering the next step in choosing my treatment became very important to me, as it gave me time to thoroughly investigate the options available to me.

Of course, the first step was to discuss the matter thoroughly with my wife, Pamela, who had spent almost her whole working life employed as a scrub nurse or as an operating room manager. Not very participatory are wives who are retired nurses!

She did concur with me that I should spend as much time as possible thoroughly researching each realistic available treatment option. The guide referred to above, was an excellent starting point. It covers the whole gambit of Localised Prostate Cancer including an array of questions that need to be asked of the medical professional.

My brother, who had been diagnosed with prostate cancer some 15 years earlier, was my first port of call. I had a basic understanding of his treatment, but it was time to find out more specific information. His PSA was then similar to mine at 8.0 and tests showed no signs of the cancer having migrated external of the prostate. He had had exposure to Chinese medicine prior to his cancer diagnosis and decided to undertake an ongoing course of herbal treatment prescribed by his specialist (who offered conventional treatment as well as Chinese herbal solutions). After 18 months of herbal treatment, his PSA was still elevated, but was not increasing. I am not sure what the catalyst was, but he decided to see Dr S, one of Sydney's leading prostate cancer specialists.

He recommended that my brother undergo high dose rate brachytherapy via the temporary insertion of radioactive-tipped needles into the prostate. This was to be followed by a 6-week course of x-ray radiation. This treatment regime was concluded in early 2003, after which his PSA level dropped over some months, to below 2 ng/ml. This level is generally regarded as men being clear of prostate cancer. He continued to have twice yearly PSA tests done, which were all below 2 until October 2008, when his PSA was up to 3.5, then by October 2009 to 9.28. Clearly, some cancer cells had survived the high dose rate brachytherapy and the follow up x-ray radiation.

His urologist advised that he was not a candidate for further radiation treatment as his urethra (the tube from the bladder to the penis) had become too brittle due to its radiation exposure. He was put on a course of Zoladex®, which is a hormonal therapy, called androgen deprivation therapy or ADT. Over three months this reduced his PSA to 0.51.

ADT causes an increase in the oestrogen to androgen ratio in the body lowering the testosterone and can be accompanied by side effects such as hot flushes, lack of libido and erectile strength, breast swelling and, in some cases, nausea. It is usually only taken continually for six months with a similar length break, before one can resume treatment for a further three- or six-month period. Continuous usage is suggested to reduce its ongoing effectiveness.

From 2011 to 2012, his PSA again increased from 0.78 to 7.94. He began another round of ADT (Zoladex®) and again reverted to Chinese herbal treatment. He also added a course of acupuncture to his treatment program. The herbal treatment was designed to strengthen his T-cells which are the immune system's 'cancer fighters'. This treatment program cost him about US$7,000 (A$10,000) a year. His PSA remained under 1.0 until September 2013, when it nudged up to 1.43. By June 2014, it had risen to 4.55 ng/ml, which started to set off alarm bells. By 2016, his cancer had progressed to the metastatic castration resistant stage, which is very serious. In fact, he was told that he had only two years to live. Eighteen months ago, he underwent an experimental course of Lutetium-177 PSMA ligand therapy which dropped his PSA to near zero. He had two follow-up Lutetium-177 injections in December 2018 and February 2019 after his PSA again started to rise into the teens. It has recently risen to 100 and now 315.

The possibility of me wanting to undergo brachytherapy with needles, dropped down the list of possible treatments, even though this point of view was based on a sample of only one.

A close friend, John, now 84, had twelve years previously been one of the first Australians to undergo Proton Beam Therapy (PBT) at the Loma Linda University Medical Centre in California, USA. This form of radiation therapy uses protons to irradiate the prostrate rather than photons that are used in all forms of x-ray radiation. The proton beam is created from hydrogen atoms in a cyclotron that accelerates the protons to about 100,000 miles per hour (160,000 kilometres per hour). The proton beam line, as it is called, is focussed via each hip joint to the prostate. It is considered to be the least damaging of all radiation techniques to the tissue that surrounds the prostate such as the bladder, rectum, seminal glands, etc. John returned from Loma Linda with absolutely minimal peripheral damage and a PSA that quickly dropped below 2. Subsequently, he became the product advocate for a Sydney-based company, who plan to build a PBT facility in Brisbane, Australia. However, Australia is likely to see its first facility in Adelaide, South Australia, which should be operational by 2021.

Only 62 such facilities exist internationally at this time, with only one in the Southern Hemisphere in Cape Town, South Africa (which only treats eye and brain cancers). Around the world, more than 20 new facilities are presently being built or are in the planning stage.

The drawback of Proton Beam Therapy to Australians, and others distant from a facility that accepts foreign patients, is the cost of the treatment, accommodation and travel and the minimum of 7 weeks (usually 10 weeks) duration of the treatment. Costs range from US$40,000 to more than US$100,000.

I continued to search the internet for information on all the realistic alternatives available to me. There is a massive array of information available and it became a serious task to decipher fact from fiction. I should explain that my disposition causes me a need to obtain as complete a picture of things as possible. Working in science for 46 years sharpened my determination to gather all pertinent facts before deciding on a course of action. I found that the medical profession, in general, only want you to know what they think you should know. This has happened to me time and time again and I find these characteristics of (many) doctors frustrating.

My internet search saw my interest in two techniques escalate to the fore. These were Proton Beam Therapy (PBT) and High Intensity Focussed Ultrasound (HIFU). The latter technique has been around since the late 1990’s with two machines being available at that time; the Sonoblate® from Focus Surgery Inc., Indiana, USA and the Ablatherm® from EDAP TMS S.A., Lyon, France. The latter is widely used in Europe and has subsidiaries in Italy, Germany, USA, Japan, Korea and Malaysia. The Sonoblate is used more so in Japan, Australia and other countries. A further HIFU machine is made by a Chinese manufacturer with more than 165 hospitals in China using the local machine. The technique involves heating the prostate via an ultrasonic probe placed in the rectum. It is over in a couple of hours and outcomes are generally excellent.

My research was interrupted when Pam and I journeyed to South Africa to visit friends and relatives. It also allowed me to attend the 50th year Reunion of the Class of 1962, at the Grey High School in Port Elizabeth. A great time was had over the four-day celebration which culminated in attendance at the Grey 1st XV Rugby team taking on a visiting team from Cape Town. Four of my closer school chums and I sat together to watch the match and I soon discovered that we all had become victims of prostate cancer. Roy had had brachytherapy seeds implanted; 'Michael' had had a prostatectomy; Graham had radiation; John didn't want to be specific about his treatment; and I still had to decide my treatment option.

Roy could not urinate for six weeks after his treatment and had to self-insert a catheter to do so. 'Michael' was substantially impotent; Graham had unspecified problems an I suspect John also was not firing on all cylinders. This information again reinforced my desire to make the right choice to manage my condition.

Whilst I was in South Africa, I checked with National Accelerator Centre attached to Tygerberg Hospital, near Cape Town, as to whether or not they had started doing prostate cancer treatment with their proton beam system. Unfortunately, they still focus entirely on cancers of the head and brain stem. If I could have been treated there, I would have had free accommodation at one of Pam's relatives, who lives nearby the Centre!

On our mutual returns from our travels, my first urologist and I discussed options. He preferred to do a complete prostatectomy (his speciality!), but I wanted a second opinion from a highly credentialed urologist at a Sydney cancer institute with whom I was familiar. Dr L was also one of only a few practitioners who practice the HIFU procedure.

I now side-track to look at what prostate cancer is, how it is diagnosed and assessed, and to provide information on the latest treatments available. In Chapter 24, I resume my journey to discover the best treatment option available to me.

Chapter 2.

What is Prostate Cancer?

Cancer is a disease in which cells in the body grow out of control. When cancer starts in the prostate, it is called prostate cancer. This malignant cell growth can be localised or advanced. Localised prostate cancer refers to those cancers that have not grown beyond the prostate. They generally have few or no symptoms and often do not develop into advanced prostate cancer. Advanced prostate cancer generally refers to cancers that have spread beyond the prostate into surrounding tissue and/or into the bones or other parts of the body including lymph nodes. The book referred to in Chapter 1, divides advanced prostate cancer into two groupings: locally advanced prostate cancer and advanced prostate cancer. They suggest that locally advanced prostate cancers are those cancers that remain in the immediate region of the prostate (or in the wall of the prostate). Advanced prostate cancers are those that have spread beyond the prostate into the seminal glands and/or the lymph nodes. When advanced prostate cancer spreads to the bones and distant organs it is referred to as metastatic prostate cancer.

The first two editions of this book focused substantially on localised and advanced prostate cancer, or as is often stated, prostate cancer that is ‘still in the box’ or in the region immediately adjacent to the prostate. Metastatic prostate cancer is a far more challenging progression of the disease that requires immediate specialist attention. This edition of the book provides more details on metastatic castration-resistant prostate cancer that is often life-threatening.

Apart from skin cancer, prostate cancer is the most common cancer in Australian men. I find the ignorance and/or disinterest displayed by many men in the 60 to 75-year age group about prostate cancer quite remarkable.

It would probably be beneficial to many readers, for us to have a look at what constitutes the prostate. It is a part of the male reproductive system, which includes the penis, the prostate, the seminal glands, and the testicles. The prostate is located just below the bladder and in front of the rectum. It is about the size of a walnut and surrounds the urethra (the tube that empties urine from the bladder). It produces fluid that makes up a part of semen. As a man ages, the prostate tends to increase in size. This can cause the urethra to narrow and decrease urine flow. This is called benign prostatic hyperplasia (often referred to as BPH), and it is not the same as prostate cancer. Men may also have other prostate changes that are not cancer.

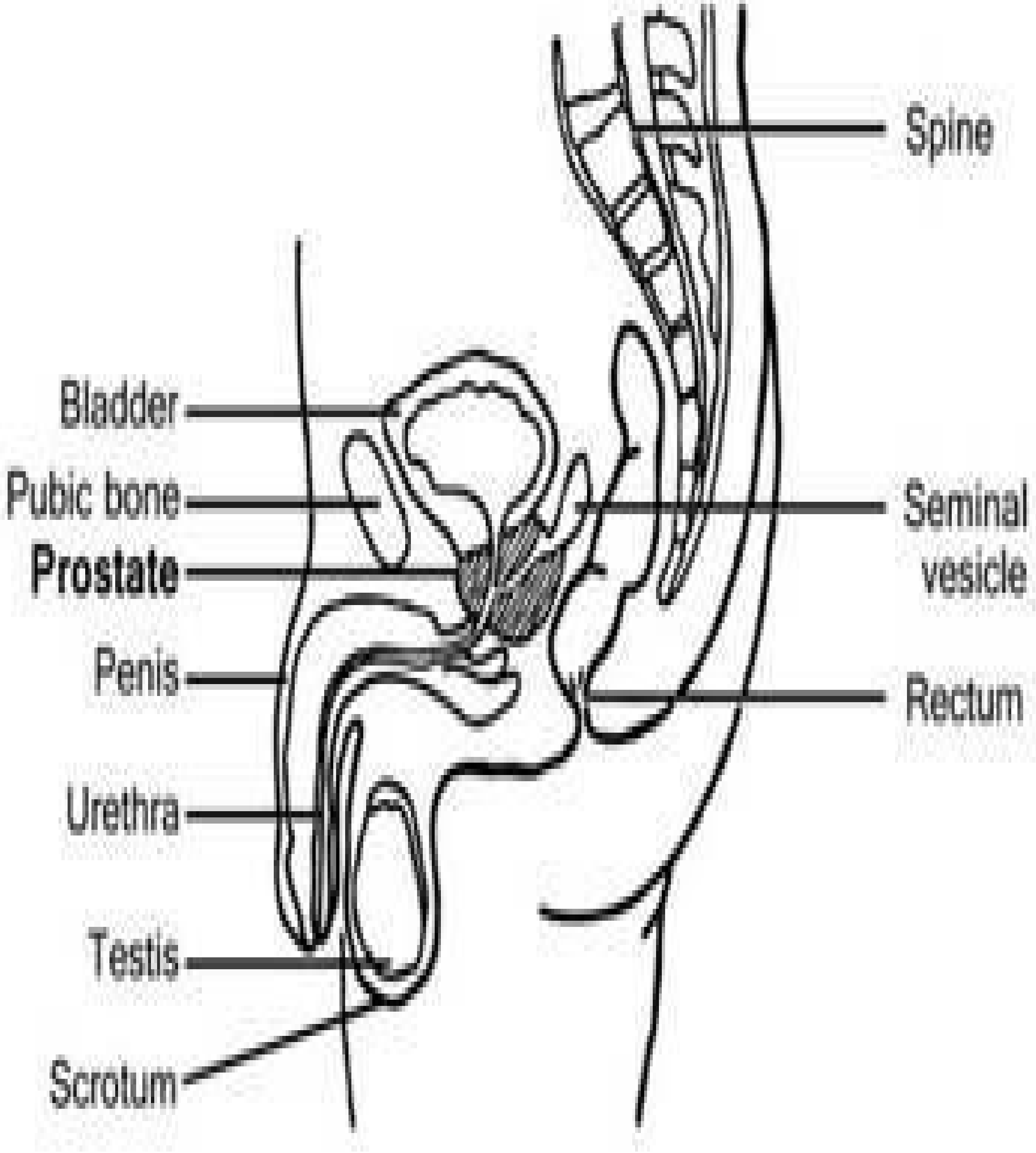

Spine
Bladder
Pubic bone
Prostate
Seminal vesicle
Penis
Rectum
Urethra
Testis
Scrotum

Image: Courtesy of Wikipedia

This diagram shows the location of the prostate, in front of the rectum and just below the bladder. Let’s look at the anatomy of the prostate. When looking at the prostate from the front, it can be is divided into four zones. These are:

The outer peripheral zone (PZ), which contains between 70% - 80% of the glandular tissue (in young men). The volume of the PZ increases from the base to the apex of the gland. (The PZ is the major region where about 90% of malignancy starts and progresses).

The transition zone (TZ) surrounding the urethra which contains about 5% of the glandular tissue. (About 10% of malignancy develops in the TZ, but is usually a less aggressive cancer. The TZ is the region where benign prostatic hyperplasia develops and then invades the central zone).

The central zone (CZ) which has about 20% of the glandular tissue.

The anterior (fibro muscular) zone (AZ) or stroma, which contains no glandular tissue.

Prostate Zones

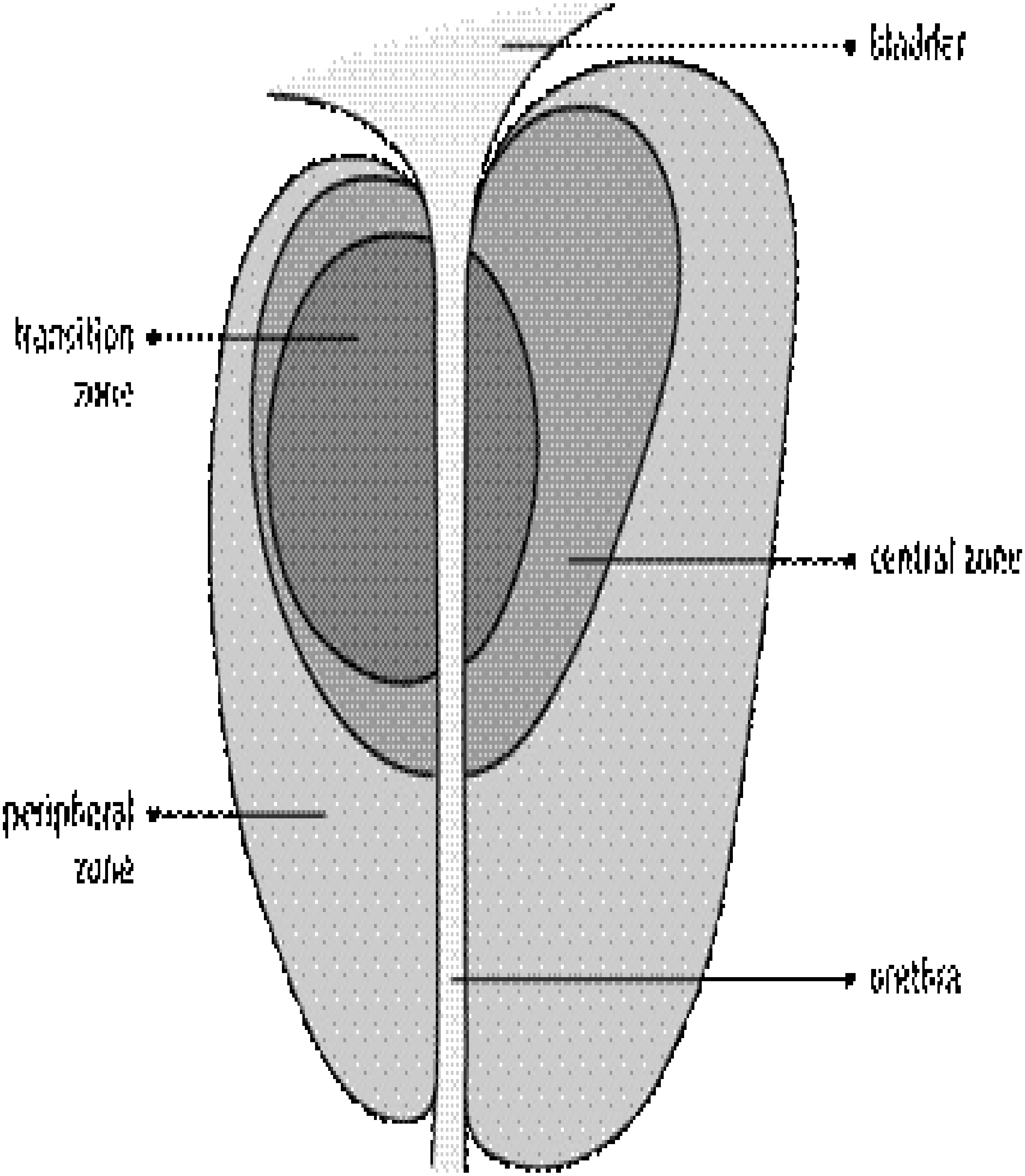


Image: © Canadian Cancer Society 2014

Many medical publications and doctors refer to ‘lobes’ rather than ‘zones’. They correlate broadly as follows:

Anterior lobe (or isthmus) – roughly equates to part of the TZ

Posterior lobe – roughly equates to the PZ

Middle or median lobe – roughly equates to part of the CZ

Lateral lobe – spans all zones.

Prostate cancers usually commence in the glandular tissue of the prostate, with about 70% originating in the PZ, about 25% in the TZ zone, and 5% in the central zone. It is very difficult for imaging to separate, the TZ from the CZ. As a result, these two zones are often referred to together as the central gland.

The prostate does not have a capsule, rather an outer band of fibro muscular tissue that surrounds it. It is integrated with the muscles of the pelvic floor, which contract during the ejaculatory process. The outer layer of tissue in the rear and rear-sides of the gland are more ‘capsule-like’ and are visible as a layer of thin tissue on T2-weighed MRI images. The ‘capsule’ is important for the assessment of possible extra-prostatic capsular extension (ECE) in DRE diagnosis. Hardness, irregularities, bulges, etc. in the capsular tissue suggest a tumour within the prostate or its spread outside the confines of the prostate.

The neurovascular bundles ‘wrap’ around the prostate and are seen at the 5-o'clock and 7-o'clock positions in reference to the prostate on imaging. At the top and bottom of the prostate the nerve bundles have branches that penetrate into the capsule. These pathways provide a route for extra-prostatic tumour extension into the neurovascular bundles.

Roughly 20,000 men are diagnosed with prostate cancer each year in Australia with around 3,000 dying from the disease. The good news is that this number is not growing, probably due to increased early detection and post detection medical intervention and treatment. This compares to about 240,000 men being diagnosed each year in the USA. According to the American Cancer Society, deaths attributed to prostate cancer in the USA in 2018 totalled 29,430. This number is likely to increase significantly in coming years due to the active discouraging of PSA testing by governmental panels and medical associations. More information on this shortly.

Age is a significant factor in the incidence of prostate cancer. Only a handful per 1,000 men under the age of 50 are diagnosed with prostate cancer, with the detection rate growing to 24 per 1000 in 50 – 59-year olds; 73 per 1000 in the 60 – 69 age group; increasing to 94 in the 70 – 79 and 93 in the 80 – 89 age groups.[1]

Many men diagnosed with early stage prostate cancer, do not necessarily need active treatment. Active surveillance is a commonly recommended way forward.

It is not known what causes prostate cancer to take hold in some men, but not in others. There is a view that diet is a factor in the evolvement of prostate cancer. We explore this further in Chapter 20. There are significant differences in the prevalence of prostate cancer between African-Americans (high prostate cancer) and Japanese (low prostate cancer). Clearly the dietary habits of these two groups are significantly different. About 10% of men who have prostate cancer who have a father and/or brother with early-diagnosed prostate cancer (50 - 59 years old), appear to have a pre-disposition to prostate cancer. This pre-disposition appears to be due to inheriting faulty cancer protection genes, rather than genes themselves causing the cancer. Considerable research is enhancing understanding of the effect of genetics on prostate cancer and the development of other types of cancer. What is clear is that if you have a father with an early prostate cancer diagnosis your chance of developing prostate cancer is doubled and with two near relatives with early prostate cancer diagnosis, your chances of prostate cancer rise seven-fold.

Generally, prostate cancer is slow to spread. When detected, it might already be well advanced. The following main possibilities exist:

The prostate cancer is confined to the prostate only (it’s contained ‘in the box’). This is referred to as localised prostate cancer. Time is on the patient’s side, due to generally slow progression of the disease.

It may have spread to other tissue outside the prostate, such as the seminal vesicles. This is often referred to as localised advanced prostate cancer.

Spread to nearby organs sees it called advanced prostate cancer.

Spread to the bones, liver and elsewhere is regarded as metastatic prostate cancer.

The last three possibilities listed above, need urgent medical intervention.

We deal with castrate-resistant prostate cancer (both metastatic and non-metastatic prostate cancer, epithelial prostate cancer and oligometastatic cancer later in the book. Metastatic hormone-sensitive prostate cancer (mHSPC), refers to prostate cancer that still responds to androgen drug therapy. Patients with newly-diagnosed metastatic disease tend to have a poorer prognosis, resulting in a need for new treatment options.

From around the age of 50 onwards, most men start to have some difficulties in urinating. They find themselves:

Getting up during the night to pass water (once at first; then twice and eventually more often).

Not being able to ‘start’ to pass water when one needs to go. It’s embarrassing to stand at a urinal for up to 5 minutes counting (silently!) from 1 to 100.

Similarly, when the flow stops and starts.

Occasionally, with an over-powering need to urinate immediately.

The cause of much of the above is benign prostate hyperplasia or BPH.

(See below). Urologists often treat this condition by surgical intervention by doing a procedure called a trans-urethral resection (TURP) of the prostate. I had this ‘partial rebore’ to improve urinary flows before my radiation treatment.

More details on this procedure in Chapter 26.

Benign prostate hyperplasia continues to be treated with drugs (Avodart®-dutasteride, etc.) to help men improve their flow with most men not requiring physical intervention. A new device is now being used in the USA, Australia and other countries, that uses steam to kill much of the prostatic tissue that is ‘pinching’ the urethra and as such impending urine flow. This USA-manufactured device is the Rezum® system. Radiofrequency energy is applied to a few drops of water in a hand-held probe, to create vapor (steam). The water vapor is injected into the prostate tissue that is blocking the flow of urine from the bladder, where it immediately turns back to water, releasing the energy stored in the vapor into the cell membranes. At this point, the cells are gently and immediately damaged, causing cell death. Over time, the body absorbs the treated tissue through its natural healing response. More details are accessible via Appendix 3.

When prostate cancer is at an advanced stage, symptoms start to emerge which may include pain during ejaculation; burning when passing water; inability to empty the bladder completely; blood in urine or semen and/or continuing lower back, pelvis or hip pain, or stiffness. A reduction in the quality of holding an erection also occurs in some cases.

Once prostate cancer is diagnosed, most men want to be rid of the disease quickly, by pursuing early treatment. According to the American Cancer Society, the bias toward treatment in the U.S. contrasts sharply with other countries. For example, an estimated 20 – 30% of European men choose active surveillance compared with only about 5-10% of American men. This early intervention mentality is frustrating to Otis Brawley MD, then chief medical officer of the American Cancer Society, who stated at an AACR conference in early 2014: “One of the problems I’ve had with this frenzy of prostate cancer screening and treatment over the last 25 years, is that we’ve actually impeded scientific development of the new markers we need to figure out the cancers that kill versus the cancers that don’t kill.”

Prostate cancer is considered to be controlled by small genetic changes that vary from male to male. Most men diagnosed with the disease, present with non-life threatening or indolent prostate cancer. A lesser number are found to have aggressive disease that, over time, becomes life threatening. This variance in the disease is considered to be due to genetic differences between individuals.

It is now possible to determine at the genomic level, with high certainty, which cancers are likely to be life-threatening and which are not likely to be dangerous. More details on genetics and diagnostic testing follow later in the book.

Chapter 3.

How is Prostate Cancer Detected?

Testing

Two tests are commonly used to screen for prostate cancer. They are a digital rectal examination (DRE) and a prostate specific antigen (PSA) test. Let’s look at them more closely.

Digital rectal exam (DRE):

The prostrate is sited immediately adjacent to the rectum wall. The doctor inserts a gloved, lubricated finger into the rectum to estimate the size of the prostate and feel for lumps or other abnormalities. The DRE can only feel part of the prostate gland and that is the posterior zone adjacent to the rectum. Lumps or other abnormalities present in the anterior region or other prostate areas, which are not reached during the rectal examination, would be missed.

Prostate specific antigen (PSA) test:

This test measures the level of PSA in the blood. The PSA is a protein produced by cells in the prostate. Its primary function is to help keep the semen in a liquid form enabling the sperm to swim. The levels of PSA can rise due to a number of reasons including the presence of cancer. The levels of PSA in the blood can be higher in men who have prostate cancer. The PSA level may also be elevated in other conditions that affect the prostate. The most frequent benign prostate condition that causes an elevation in PSA level is prostatitis - inflammation of the prostate - and benign prostatic hyperplasia (BPH), which we have already read, is the enlargement of the prostate. Some drugs used to treat BPH have been found to lower PSA levels.

As a rule, the higher the PSA level in the blood, the more likely a prostate problem is present. But many factors, such as age and ethnicity, can affect PSA levels. Some prostate glands make more PSA than others. PSA levels also can be affected by:

Certain medical procedures

Certain medications

An enlarged prostate

A prostate infection

Ejaculation within 24 hours of having the test done

Bicycle riding.

Most doctors prescribe a urinary test to check for a possible infection when ordering a PSA test. An infection is likely to elevate the PSA result.

In a large study reported in 2004 by Thompson, et al., it was found that 15% of men who had a prostate that felt normal on examination and a PSA less than 4, went on to be confirmed later in the study by biopsy of having prostate cancer. Of the 15% who had prostate cancer, 33.7% of the 15% had a final PSA of less or equal to 2.0 ng/ml. Participants were aged from 62 to 91 years old.[1] Of course, the higher the age the greater the likelihood of a positive finding. The Boots WebMD web site's Prostate Cancer Guide reports men who have a 'normal' PSA level below 4 ng/ml have a 15% chance of having prostate cancer. Those with a PSA level between four and 10 have a 25% chance of having prostate cancer and if the PSA is higher than 10, the risk increases to 67%.[2,3]

Your doctor is the best person to interpret your PSA test results, because, as we have seen, many factors can affect PSA levels. If the result of the test is abnormal, further testing is needed to see if there is a cancer present. If prostate cancer is suggested as a result of screening with the PSA test or DRE, it will probably be at an earlier, more treatable stage than if no screening were done. If it is decided to do another PSA test a few months down the track, it is important to ensure that the test is done in the same pathology laboratory that did the first test, as there is significant variability in PSA testing between laboratories.

A recent study quantified the number of men with low or very low PSA who were found to be harbouring prostate cancer: 6.6% of patients with a PSA < 0.5 ng/ml and 26.9% of patients with a PSA 3 - 4 ng/ml. This data contradicts the > 2 ng/ml or > 4 ng/ml (age and family history dependant) levels espoused by doctors and their association guidelines.

Today most doctors considered PSA levels of 4.0 ng/ml and lower as normal. Therefore, if a man had a PSA level higher than 4.0 ng/ml, doctors would often recommend a prostate biopsy to determine whether or not prostate cancer was present. If there is a family history of prostate cancer and if the PSA level is higher than 2.0 ng/ml, doctors are likely to prescribe regular PSA testing. Neither the PSA test nor the DRE is 100% accurate. These tests can sometimes have abnormal results even when cancer is not present (known as false-positive results). Normal results can also occur even when cancer is present (known as false-negative results). False-positive results often lead to some men having a prostate biopsy (with its attendant risks of pain, infection, and bleeding) when they do not have cancer. False-negative results can give some men a false sense of security even though they actually have cancer.

Another important issue is that even if DRE and/or PSA screening detect cancer, doctors aren’t able to ascertain if the cancer is aggressive or passive. Some prostate cancers grow so slowly that they would probably never cause problems or show symptoms of cancer being present. Because of an elevated PSA level, some men may be diagnosed with a prostate cancer that they would have never even known about at all. It would never have led to their death, or even caused any symptoms.

Today, it would be highly unlikely that a doctor would recommend aggressive intervention such as surgery or radiation treatment without the patient undergoing a biopsy. Only after the results of the biopsy are known, can the doctor (urologist) determine the extent of the cancer and it level of ‘aggressiveness’. More details on biopsy testing follow later in this chapter.

Doctors agree that the PSA blood test is not a perfect test for the early detection of prostate cancer. As indicated earlier, a low PSA test value might cause some cancers to be missed, and in other cases it is elevated when cancer isn't present. A PSA result of less than 10 ng/ml, suggests the cancer is likely to be confined to the prostate (‘in the box’), with 30 ng/ml or higher readings suggesting that the cancer might have spread beyond the prostate. Even in cases were the PSA is > 10 ng/ml, the statistics suggest that the likelihood of prostate cancer being present is less than one in three in one study and one in two in another.[4]

Your doctor may order a follow-up PSA test that measures ‘free’ PSA (the standard PSA test measures ‘total’ PSA). This test measures the amount of PSA in the blood that is ‘free’ (not bound to other proteins) divided by the total amount of PSA (free plus bound). This is usually expressed as a percentage. Low ratios (less than 15% free to total PSA) suggest a higher risk of cancer being present whilst higher ratios of above 20% free to total PSA, suggest less likelihood of cancer being present. Some evidence suggests that a lower proportion of free PSA may be associated with more aggressive cancer.

Age is a key factor in deciding on future action. DRE and PSA should be undertaken for men over 40 if there has been a family history of prostate cancer. All men over 50 should have a DRE and PSA test undertaken when having their annual physical check-up.

In early 2012, the United States Preventative Services Task Force (USPSTF) came out with an astonishing recommendation: Doctors should abandon routine PSA testing in healthy men. The USPSTF were seriously concerned about the massive over-servicing of prospective and confirmed prostate cancer patients. This included hundreds of thousands of ‘unnecessary’ biopsies, sometimes followed by surgery and radiation therapies. All brought about by elevated PSA testing results. These included some patients whose PSA had gone up from below 2 to below 4 over the year and were then subjected to radiation treatment or surgery. Clearly, these men should have slotted into the active surveillance or watchful waiting categories. It also emphasizes the need for patients to become more aware of the various procedures and the attendant risks and benefits available to them. Also, it confirms the need for second opinions to be obtained. The 2012 USPSTF report was substantially re-affirmed in May 18. Access the USPSTF full report or a one-page summary via Appendix 3.

In mid-2013, the American Urological Association (AUA) recommended that their members discontinue routine PSA testing for men in the age group 40 to 54 years old. Many doctors have no doubt heeded this call to limit PSA testing in this age group. There is a possibility that in the years ahead, many more men are going to present with prostate cancer that might be more advanced, than would have been the case under the past testing regime. Their 2013 guidelines for PSA testing were re-affirmed in 2018. Access the AUA new PSA testing guidelines via Appendix 3.

Elimination of PSA testing would triple the number of men who have advanced prostate cancer at diagnosis, claimed the authors of a retrospective review. "Our analyses suggest that, if the pre-PSA era incidence rates were present in the modern U.S. population, then the total number of men presenting with M1 (metastatic) prostate cancer would be approximately three times greater than the number actually observed," Edward M. Messing, MD, of the University of Rochester in New York, and co-authors, wrote in conclusion.[5]

PSA screening cuts deaths from prostate cancer by some 30 percent recently reported Maria Franlund, M.D., Ph.D., in Urology, at Sahlgrenska Academy, University of Gothenburg. This research was based on data of 20,000 men monitored for more than two decades. Franlund's thesis work originates from a large, population-based study that currently has the longest follow-up period of all screening studies on prostate cancer worldwide. Its results directly fly in the face of the Swedish National Board of Health and Welfare recommendation that their health services should not offer screening with PSA testing alone. Reason: over-diagnosis and over-treatment which outweighs its benefits. Dr Franlund said men in good health and with a PSA above 1.5 ng/ml should be offered continued check-ups after age 70.

It should be remembered that PSA testing and the DRE test are the basis of early prostate cancer diagnosis. The ‘over-servicing’ by subsequent treatment is an issue best controlled by the patient and his medical professionals after careful consideration of ALL the facts and alternatives present.

By mid-2016, it had become clear from a number of published studies, that the AUA decision to not recommend routine PSA testing had been in error. The percentage of men presenting with high risk disease had started to track the increase in plus 75-year-old cases (a group who have been the subject of ‘no initial PSA testing’ protocol since 2011). Surprisingly, the 2013 AUA guidelines, like the USPSTF, were re-affirmed in 2018.

Some men have significantly enlarged prostate glands brought about by benign prostate hypertrophy (BPH) or naturally. The average prostate size for a man aged 45 is around 40cc (cubic centimetres or millilitres). (My prostate at the time of diagnosis was considered small at 29cc – something of a let down to my manliness!). It is thought that with much larger prostates, the ‘normal safe’ PSA level of 4 ng/ml, should be higher. Some doctors overlook this factor or are unaware of the benefit of calculating a PSA Density figure that takes into account the size of the prostate. The PSA density is a simple mathematical calculation derived from the division of the PSA value by prostate volume. The higher the PSA density, the greater is the likelihood of prostate cancer being present. A density of greater than 0.15 is more suggestive of prostate cancer. A density between 0.07 and 0.15 is in the grey area, with a density of under 0.07 is more suggestive of non-cancerous disease.[6]

If the DRE suggests to the doctor that you may have a prostate infection, or the lab analysis of your urine done at the same time as the PSA test shows an infection to be present, the PSA test should be repeated a few weeks later after the infection has been treated by a course of antibiotics. Similarly, should prostatitis (inflammation of the prostate gland) be present, a repeat PSA test should be done some weeks after the condition has been successfully treated.

It is also important to have your PSA sample sent to the same pathology lab on each occasion as there is often significant variance in results from lab to lab. My doctor provided me with a copy of the laboratory report after each PSA test which lists the results of my last ten PSA results.

It is worth noting that the vast majority of men currently diagnosed with low-risk prostate cancer undergo surgery or radiation treatment, although there is only a three percent chance that their disease will become life-threatening.

New and Future Developments in PSA Testing

Considerable research over the last decade has led to improvements in the PSA testing regime. One approach has been the development of new tests based on other tumour markers. Several newer blood tests seem to be more accurate than the PSA test, based on early studies. Some of these tests are not yet in general use; others are increasingly being used. They include blood and urine-based tests.

Another research development has focussed on an abnormal gene change found in prostate cells. This gene change is found in about half of all localized prostate cancer. It is rarely found in men without prostate cancer. Various urine tests detecting gene changes are now undergoing regulatory approvals.

Many research studies, both of short or long duration, are underway. Prostate cancer is often a slow-growing cancer, so the effects of screening in these studies may become clearer in the coming years.

One genetic test that reached the market in the USA and other countries (including Australia). a few years ago, is the Progensa® PCA3 test marketed by Gen-Probe Inc. of San Diego, California. The PCA3-molecule was discovered some years ago, followed by the finding that concentrations of the PCA3 molecule are 100 times higher in prostate cancer cells than in normal prostate cells. In technical terms, this molecular assay detects the mRNA expression of the DD3 gene expressed in prostate cells. In recent studies, it was shown to have a specificity of 78% and a sensitivity of 57% in cancer vs. non-cancer. (By way of comparison, the PSA test, at modest elevations, has a specificity of as low as

20%, but rises to as much as 50% at levels ≥10 ng/ml).

As a result of a digital rectal examination (DRE), which includes the massaging of the prostate by the doctor, prostate cells, including potentially cancerous cells, are released into the urine. These cells can be detected in urine samples obtained after the DRE procedure is completed. This process is much less invasive for the patient than a prostate biopsy.

The PCA3 score is reported as a quantitative PCA3/PSA mRNA ratio x 1000 to normalize PCA3 to the amount of prostate RNA present in the urine sample. In cases, where insufficient PSA mRNA is present, are considered inconclusive. A score equal to or greater than 25 is considered positive. A positive result suggests an increased likelihood of a positive prostate cancer result being returned on biopsy.

In the USA, we have seen a further development of the PCA3 diagnostic test into a three-parameter test called MiPS or Mi-Prostate Score. The MiPS test is an early detection test (pre-biopsy) for prostate cancer that combines the amount of serum PSA, with the amounts of two genes in the urine. These two genes, TMPRSS2: ERG and PCA3, are specific for prostate cancer, meaning they are rarely present at high levels in the urine of men without prostate cancer. The MiPS combines serum PSA, urine TMPRSS2: ERG (also known as T2: ERG) and urine PCA3 to predict the likelihood of a patient having a positive prostate cancer determined by biopsy. The test also predicts the patient’s risk of having potentially aggressive prostate cancer. The MiPS test was developed by the University of Michigan Health System and validated on almost 2,000 patients. The MiPS test is designed to help doctors and patients make a shared decision after PSA testing about whether to monitor PSA levels or pursue a prostate biopsy. An interesting set of Questions and Answers on MiPS can be accessed via Appendix 3. This test presently costs US$783 in the USA.

In 2012, the FDA gave approval for the marketing of the Prostate Health Index or phi Test (Beckman Coulter) for patients with a PSA in the range 4 ng/ml to 10 ng/ml.[7] This test uses a mathematical formula that combines total PSA, free PSA, and p2-PSA (a protein associated with prostate cancer) data to provide a Prostate Health Index level. In clinical trials among men with a standard PSA level between 2 and 10 ng/ml, the average (mean) phi scores were 34 for men who went on to have negative biopsies and 49 for men who went on to have positive biopsies, respectively. When a doctor asks for the PHI test, they get a report giving Total PSA, free PSA, p2-PSA and the Prostate Health Index. The Prostate Health Index is included in the National Comprehensive Cancer Network (NCCN) Guideline for Prostate Cancer Early Detection as a blood test to improve specificity for prostate cancer detection.

In 2013, Sanda and colleagues showed that not only did phi outperform free and total PSA for prostate cancer detection, but it also improved the prediction of high-grade and clinically-significant prostate cancer. In 658 men with PSA levels of 4 to 10 ng/ml from their multicentre study, it showed that a significant relationship exists between phi and the Gleason score on prostate biopsy. Additionally, 25% of the study population had phi levels < 27, and only a single patient in this phi range had a biopsy Gleason score ≥ 4+3 = 7. These combined findings suggest that the use of phi could significantly reduce unnecessary biopsies and the over detection of non-lethal disease. The test could still provide false negatives and false positives. The test costs about $80 in the USA.

In 2014 OPKO Diagnostics introduced a new test, namely the 4K score test. The 4K score test gives a more accurate prediction of risk for a Gleason score of 7 or higher on biopsy than the PCPT calculator (version 2.0) (more on this calculator in the following chapter).[8] The 4K score blood test is an assay panel that combines three PSA measures (total, free, and intact) with another prostate-specific measure, human kallikrein 2 (hK2), in an algorithm that takes into account a patient's age, digital rectal exam result, and previous biopsy status. The test offers the same limitations as the phi test, when the result is considered for an individual patient. False positives and false negatives are likely in some instances, which make a precise decision as to whether to biopsy or not to biopsy, harder. However, it might be possible to consider having two standard PSA tests done (the second a couple of months after the first), and then a phi test followed by a 4K score test. The two PSA test results, together with the other patient metrics, provide a cancer risk assessment on the PCPT calculator. Should all four values suggest a likelihood of a Gleason score of 7 or higher being found on biopsy, it is a pretty clear case to have a 10 core (or greater) biopsy as soon as possible. The 4K score test has recently been recognised in the NCCN Guidelines and costs about US$760.

A new office-based PSA test has recently been approved by the FDA. The Sangia Total PSA Test samples blood from a finger prick similar to a diabetes check. Results are available in less than 15 minutes using the Claros1™ analyser. The results obtained from a clinical study in the USA showed that the test is safe and effective and gave comparable results to the two most common blood-based PSA tests used today. It is expected to be used when a DRE test is done. A clear benefit of the test is the rapid availability of a result, which gives the doctor an opportunity to discuss treatment options.

Ccheck, a new test for early cancer detection under development by Anixa Biosciences, identifies patients with aggressive prostate cancer, and helps decide who should be recommended for a prostate biopsy, potentially reducing the number of unnecessary biopsies. The test objectively analyses flow cytometry data using machine learning to predict whether a subject is at higher risk for having an aggressive form of prostate cancer (Gleason ≥ 4+3). In a recent study of 203 subjects recommend for biopsy, approximately 105 procedures could have been avoided. The product development continues.

The hunt for new diagnostic tests based on non-invasive biomarkers for prostate cancer continues unabated. These urine-based tests are urgently needed to complement PSA screening for the early identification of aggressive prostate cancer. Such tests will guide decision making for initial diagnostic prostate biopsy or repeat biopsies of low-risk patients on active surveillance.

A paper[17] published in the journal JAMA Oncology (2016 March 31) reported on a urine assay (the ExoDx™ Prostate IntelliScore urine exosome assay) that successfully differentiated between Gleason Score 6 or less and Gleason Score 7 or higher values. (More on biopsies and the Gleason Score later in this chapter). Of the 519 patients involved in the study, 27% would have avoided the need for a biopsy. Access more details via Appendix 4.

The ExoDx™ Prostate IntelliScore (EPI), now available widely in North America, is a simple, non-invasive urine test that accurately predicts the aggressiveness of prostate cancer. Bio-Techne Corporation recently confirmed the NCCN decision to include EPI as a recommended test in their Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection. The test detects three important genetic biomarkers that can identify the aggressiveness of prostate cancer. Using this assessment, your physician can determine whether or not you should undergo an initial biopsy or continue to be monitored under an active surveillance regime.

"Men over 50 with an inconclusive PSA level between 2 and 10 have another course of diagnosis before yielding to a painful and risky prostate biopsy," stated Chuck Kummeth, President and CEO of Bio-Techne.

SelectMDx® is a three-gene (HOXC6, TDRD1 and DLX1), proprietary urine-based, molecular diagnostic test that offers a non-invasive liquid biopsy method to assess a patient's risk for prostate cancer. SelectMDx® helps identify men at increased risk of harbouring aggressive, potentially lethal, prostate cancer who may benefit most from a prostate biopsy and earlier detection. The test delivers a negative predictive value (NPV) of 98% for clinically significant disease, helping to reduce the need for MRI procedures and invasive prostate biopsies by up to 50%, thereby reducing healthcare costs. The test has been included in the 2018 European Association of Urology clinical guidelines. SelectMDx® is available in the US and all EU member states with nearly 19,000 men being tested in 2018.

Another urine-based test under final development is Prostac® which is able to accurately differentiate between benign and aggressive prostate cancer. “Prostac is a non-invasive, urine-based test that will resolve numerous flaws in existing prostate cancer screening methods,” said Charles Oyesile, MD, PhD, NucleoBio’s CEO and co-founder.

IsoPSA™, a blood test developed by Cleveland Diagnostics, detects cancer-derived PSA, according to the results of a recent U.S.-based study. It was found to be more accurate in diagnosing prostate cancer than a conventional PSA test and will reduce the need for biopsies by nearly half. These findings were published in the Journal of Urology (June 19). (If 1,000 patients were biopsied, the assay would have reduced the number of unnecessary biopsies from 705 to 402 (43%) with only 22 missed high grade cancers, of which 7 would have been Gleason sum 4 + 3 or higher). During the clinical study, the combination of IsoPSA and mpMRI proved 86% accuracy in pre-biopsy identification of high-risk prostate cancer. The Cleveland team’s lead researcher, Dr. Eric Klein said, “That’s pretty good, certainly much better than standard PSA and free PSA.” It is expected to become available in Q4/2019, and nationally available following approval/clearance by the FDA in 2020. It promises to be a highly desirable addition to the diagnostics tools available to diagnose prostate cancer.

Genetic Risk Testing before a Prostate Biopsy

As all body cells grow and divide, they make copies of their DNA. Minor errors occur in this cell replication process, but healthy cells are able to recognise and correct or destroy these faulty cells. Men with inherit abnormal genes lack the ability to repair these abnormalities which may lead to genetic damage and in time cancer. By way of example, the PTEN gene protects the body from cancer cells. When the gene stops working correctly, cancer can result. Similarly, with the BRAC1 and BRAC2 gene mutations (particularly well-known in breast cancer) and other genes.

Other gene mutations associated with potentially aggressive prostate cancer are ATM, CHEK2, RADS51D and PALB2. Some physicians consider the patient’s genetic risk at this time. He/she might call for a COLOR hereditary cancer test which looks for 30 different gene mutations, including the seven listed above. This test is available in the USA for $249. This test also might alert the patient to possible genetic abnormalities in their near-family members. We will look at genetic testing more fully later in the book.

Testing after a Negative Prostate Biopsy

The ConfirmMDx®test is to confirm that the results of a negative biopsy are indeed negative. (This is due to the biopsy needle ‘missing’ cancerous tissue or very rarely, a pathology error). The use of ConfirmMDx® helps physicians decide which men are at lower risk of harbouring aggressive prostate cancer. Its use has resulted in a 65% reduction in the rate of unnecessary repeat biopsies. MDx Health presented data demonstrating the prognostic value of its ConfirmMDx®test at the AUA May 2019 annual meeting.

Testing after a Positive Prostate Biopsy

The Genomic Health Oncotype DX® Genomic Prostate Score test is a genetic test that provides a Genetic Prostate Score (GPS) after a prostate biopsy. The GPS is on the scale of 1-100, with higher scores more suggestive of less than optimal pathology. The test is generally available tor men with low or immediate risk prostate cancer on biopsy within the last three years, or in the case of a Gleason 7 (4+3) or higher result, to confirm the aggressiveness of the disease. A higher GPS score is suggestive of advanced cancer somewhere in the prostate. A lower GPS score suggests active surveillance as the best treatment option.

The other genetic tests available are based on RNA analysis of sample tissue taken from a removed prostate gland or biopsy tissue.[9]

Myriad Genetics market the Prolaris® test which is used at the point-of-diagnosis and in the post-surgery setting. At diagnosis, it can help to identify men with less aggressive cancer who may be candidates for active surveillance. In addition, Prolaris can identify patients who appear to be clinically low risk, but have a more aggressive disease that requires more extensive treatment. It is well suited for use in post-prostatectomy patients who have higher risk features after surgery to better estimate their risk of disease recurrence and therefore adjust the level of monitoring or add additional therapy. It is a genetic test measuring the expression of 31 genes involved in the important regulatory step in the development of cancer, called cell-cycle expression. The test provides a Prolaris score of 1 to 10 with a higher score indicating aggressive cancer. The patient's mortality risk doubles for every unit increase in the Prolaris score.

Testing after a Prostatectomy

The Decipher® test is a genetic test by GenomeDX Biosciences. It is used on a removed prostate to determine the probability of recurrence and the risk of metastasis after the prostatectomy. The Decipher test generates a score between 0 and 1 in 0.1 increments. The higher the reading, the higher the likelihood of recurrence or aggressiveness of the cancer.

The Prolaris test by Myriad Genetics is also used after a prostatectomy, as explained above.

Circulating tumour cells (CTCs)

CTCs are cells that have shed into the vascular and/or body's lymphatic system from a primary tumour and are carried around the body in the blood stream. CTCs are thought to represent the earliest form of metastases with CTCs presenting seeds for the subsequent growth of additional tumours in distant organs. The detection and analysis of CTCs can assist early patient prognoses and the determination of appropriate tailored treatments. Considerable research and product development have gone into bringing CTC-based assays to market. There are about a dozen CTC assays that use different techniques to deliver their results. The Epic Sciences methodology appears to me to be superior to the rest as it can characterise single cells and their response to up to 90 morphological parameters. It also looks for cell abnormalities such as duplications, deletions, and rearrangements.

****

Mutations in BRCA1 and BRCA2 genes were originally spotted some years ago in women with breast cancer. More recent research has confirmed that these faulty genes not only raise the risk of developing breast cancer, but also of ovarian and prostate cancers. The results of a major study in the May 2013 Journal of Clinical Oncology, reported that 1.2% of men with prostate cancer carry the BRCA2 mutation and 0.44% have the BRCA1 mutation. Carrying the BRCA2 mutation gives a man an 8.6 times higher risk of developing prostate cancer compared to a non-carrier. If a man carries the BRCA1 mutation, he has a 3.4-fold higher risk. The BRCA2-prostate cancers that arise in these men also tend to be more aggressive.[10]

The 2017 Philadelphia consensus-driven framework for multigene testing for inherited prostate cancer recommends the following genes be factored into management considerations: BRCA 1, BRCA 2, ATM, and HOXB13. It is advisable to discuss genetic testing with your doctors, if there is a family history of breast and prostate cancer. Genetic counselling of the patient and family members is also recommended should the patient carry one or more of the above genes.

Cancer – The Hunt for Molecular Answers and the Metabolic Theory

In 2015, The Cancer Genome Atlas (TCGA) was concluded. This enormous project, which started as a 3-year pilot study in 2006 organised and funded by the US National Institute of Health, has seen the collect of cancer and normal cells from 11,000 cancer patients. These cells, which covered 33 cancer types and sub-types, have been subjected to extremely sophisticated, genomic analysis, which has led to the discovery of many molecular anomalies and actual cancer genes.

One such mutated gene, called p53, is present in about half of all cancer types. However, most mutated genes appear at the rate of between 2% and 20% in all patients with the same cancer. It is now known that most of the mutated genes are ‘passengers’ with no apparent role in cancer cell development. There are a small number of ‘driver’ genes that are very active in cancer cell propagation. Working out which gene does what is the hard part.

TCGA has produced an enormous amount of data that is available free to the medical research community. The fight against cancer at the molecular level has been significantly enhanced by the availability of the TCGA data. On the other hand, the conclusion of this project did not yield as many molecular ‘matches’ as expected. It proved that there were huge genetic differences between same-type cancers even in tumours from the same patient. It further confirmed the complex nature of what is cancer and the difficulty of fighting the disease at the molecular level.

However, progress is being made as became evident in November 2015, when the TCGA Research Network announced the discovery of seven new molecular sub-types of prostate cancer based on known and novel genetic drivers of the disease. It is expected that detailed knowledge of these sub-types may provide prognostic and therapeutic implications.

More evidence of research progress came in June 18 when researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust found that patients with mutations in the RB1 gene in their tumours were 3.3 times more likely to die and 6.6 times more likely to relapse during the course of their study, than other men who also had standard treatment, but did not have the mutation. RB1 was the only gene found to have such an impact on survival, but mutations in two further genes – p53 and the AR gene – were associated with an increased risk of relapse on abiraterone or enzalutamide. Mutations in DNA repair genes BRCA1, BRCA2 and ATM, and in PI3K genes were relatively common, but had no impact on treatment with abiraterone or enzalutamide or on overall survival.

There is a growing number of top medical researchers who are dusting off the metabolic theory of cancer as proposed by Dr Otto Warburg, who won a Nobel Prize for this work, in 1933.

Travis Christofferson in his book “Tripping over the Truth” said:

“The metabolic theory states that cancer originates from damage to the cell’s capacity to generate energy with oxygen (oxidative energy production), with a concurrent increase in energy generation without oxygen. Oxidative energy production takes place in a cellular organelle called the mitochondria. The mitochondria are known as the cellular “power plant.” The metabolic theory of cancer contends that cancer begins with damage to the mitochondria. The cell is then forced to shift energy production to fermentation in order to survive. It is telling that this one feature of cancer, damaged mitochondria and increased fermentation is present in all cancer types. Also telling is the fact that the greater the degree of fermentation displayed by a given cancer, the more aggressive the cancer. Because a tumour cell’s mitochondria are damaged, and are therefore forced to generate energy by such an inefficient pathway, they have to consume

much more glucose to remain viable." He went on to add, "Emerging evidence suggests that all of the hallmarks of cancer can be explained by mitochondrial damage followed by a shift to non-oxidative energy metabolism. Once the oxidative energy generating capacity of the cell is impaired, the cell undergoes a dramatic transformation; important oncogenes (cancer causing genes) are switched on, initiating the uncontrolled proliferation that is the hallmark of the disease. Some degree of metabolic dysfunction has been shown to be present in every type of cancer, regardless of tissue of origin."

A Little More About Genes and Genetics

This section is a little technical. Most readers will have heard of DNA and its two-stranded double helix that was discovered in 1953. Its discovery was perhaps the most significant scientific event of the second half of the last century. DNA stands for deoxyribonucleic acid.

A gene is a unit of DNA usually located on a chromosome. It controls the characteristics that an offspring receives from their parents. Genomics is that area of science that involves the study of all the nucleotides that encode the entire blueprint of an organism. (Nucleotides are the basic structural elements of nucleic acids such as DNA). Cancer and inherited diseases are considered to be due to errors in this blueprint.

There are approximately 24,000 genes in humans, present within the 6 billion nucleotides making up human DNA (about 3 billion on each of the two strands of DNA). Cancer is considered to be due to errors in only a relatively small number of genes, about 150 to 250 genes, and these genes are associated with the specific functions of the cell being cell proliferation or growth, control of cell functions and ongoing cell behaviour.

There are only four types of nucleotides in DNA. Types G, C, T and A. Errors in the coding of a small number of these nucleotides, their absence or duplication, results in ‘rogue’ activity by the affected cells. Healthy cells have mechanisms to correctly control their activities, but in cancerous cells these mechanisms fail.

The science of epigenetics is today rapidly evolving. It considers changes that are occurring to our DNA by environmental influences. Today, we have the ability to reduce our risk of contracting diseases by maintaining healthy lifestyle habits, by reducing stress in our lives, avoiding toxins, eating quality foods and by maintaining a positive mindset.

What does all this mean? Let’s use the gene p53 to illustrate what it is all about. This gene is critical in killing off cancerous cells as they develop. It has been estimated that at any one time at least a million cancer cells exist in every healthy adult’s body. Thus, the p53 is a critical component of the body’s immune system to eliminate cancerous cells before they ‘get hold’. The p53 gene causes the cell division cycle to come to a halt when the gene detects cell abnormalities. It determines whether or not the DNA is capable of repair. If it is, it allows proper genetic expression (development). If not, it marks the cell for apoptosis or cell death. This critically important gene regulates hundreds of other genes throughout the body.

However, the p53 gene is influenced by environmental factors such as oxidative stress, which leads to an increase in free radicals in the body, which in turn lessens the ability of antioxidants to act optimally. Chronic oxidative stress, a known contributor to cancer development, can lead to an epigenetic mutation of the p53 gene. In these conditions, the p53 gene no longer has the ability to inhibit cancerous cell divisions.

The p53 protein is stimulated by zinc, but impeded by high copper concentrations and other dangerous metals such as cadmium, mercury, aluminum and lead in the blood.

Biopsy Testing

If your prostate specific antigen (PSA) test or digital rectal exam (DRE) is abnormal, doctors may do more tests to diagnose prostate cancer. These are likely to include:

A transrectal ultrasound (TRUS): A probe the size of a finger is inserted into the rectum, and high-energy sound waves (ultrasound) are bounced off the prostate to create a picture of the prostate, called a sonogram. The sonogram indicates the shape and nature of the prostate. It does not detect cancer. The ultrasound is used to ensure that samples are taken reliably from different parts of the prostate. It might also identify areas of the prostate that appear ‘suspicious” or areas determined as abnormal by DRE.

A biopsy: A series of small pieces of tissue are removed from the prostate and examined under a microscope by a pathologist to see if there are cancer cells present in the prostate tissue samples. There are generally three types of protocols used for undertaking a biopsy. These all relate to the comfort of the patient whilst the prostate tissue is obtained. Biopsy tests without sedation appear to be less common today, due to the higher number of biopsy (rods) samples taken. The taking of samples can be somewhat daunting for the patient, particularly if the urologist doesn’t have an assistant to log and identify the position of each sample taken. Under these circumstances, it could take up to 30 minutes or more for the biopsy samples to be taken and logged with the sampling probe perhaps removed a number of times and re-inserted.

Some urologists use local anaesthetics around the prostate to increase patient comfort. Today the majority of urologists do the biopsy under a general anaesthetic. After the patient is ‘put under’, the urologist uses the ultrasound probe to produce a sonogram that allows him/her to guide the insertion of a small spring-loaded needle through the rectal wall into the prostate. Usually between 12 to as many as 24 tissue samples (often referred to as cores) are taken from the prostate during an initial first biopsy. These cores are usually about the thickness of a toothpick and about 10mm long. Some urologists still only take 6 to 10 tissue samples which can increase the chance of missing the cancerous areas of the prostate.

In addition to the grade (see pages 52 - 54), your pathologist will report the number of positive cores found and probably the percentage of each which has been found cancerous. These are usually reported as percentage positive cores. For example, if 8 cores out of 24 were cancerous, you would have 33% positive cores.

It is now possible to carry out ‘targeted’ biopsies under MRI. The cost of MRI-based biopsies is higher than that of TRUS-guided biopsies. This type of biopsy is increasing in popularity, but is not widely used as yet, mainly due to urologists being committed to well-practised techniques, the time taken to complete the procedure and the lack of 3 Tesla field strength MRI machines, which give the best results. See the following section for more details on a MRI-based biopsy.

Prior to a prostate biopsy, patients should make sure that their urologist is advised of all medications that they are normally taking on a day-to-day basis. Patients who take aspirin, warfarin, or clopidogrel (Plavix®) — or other so-called ‘blood thinners’ — are normally asked to stop taking such drugs for a period of time prior to a biopsy procedure, and should discuss the appropriate time to stop taking such drugs (and when to restart them after biopsy) with their primary care physician or their cardiologist, as appropriate. I suffer from atrial fibrillation, and take Warfarin daily to prevent blood clotting. My cardiologist prescribed Clexane® as a substitute for the daily Warfarin dose in the lead up to and immediately following the biopsy. My wife enjoyed the twice daily injections into my abdomen area!

If the urologist believes that the cancer may be present in the front part of the prostate, the biopsies may be taken using a different technique, which is called the Perineal Method. This involves taking sample rods from the prostate via the area between the anus and the scrotum, which is called the perineum.

There are instances, where cancer is not detected via the first biopsy, due to low level cancer. A negative biopsy is not completely conclusive that cancer is not present. The patient’s PSA is usually monitored on a regular basis (probably 6 monthly) after a negative biopsy result. An increasing PSA result, may lead to a second series of biopsies being undertaken.

Use of a general anaesthetic dictates that the procedure is undertaken in a day clinic or hospital with a patient being discharged a few hours after the procedure is completed. Some urologists undertake the procedure with patients under sedation or local anaesthetic in their specialist rooms. The urologist will prescribe a course of antibiotics to be started before and after the procedure to lessen the chance of infection. Post the procedure, the patient is likely to experience some rectal bleeding, blood in the urine and blood staining of the ejaculate. Blood in the ejaculate should cease over the following few weeks.

Magnetic Resonance Imaging and biopsies – A quantum leap forward in technology?

Most of us have had an MRI at one time or other. If you have had one you will certainly remember it, as it’s a very loud machine! It’s also somewhat claustrophobic as you are inserted into a smallish tunnel (smaller than that in a CT scan) and sometimes have a head guard fitted. Music is often provided to deaden the noise emitted from the machine as it collects your image, slice by slice. Of course, patients with metallic implants and pacemakers are not generally able to have MRI scans.

Considerable research into the use of variances of Magnetic Resonance Imaging (MRI) to assist in the detection and assessment of prostate cancer has been ongoing for at least twenty years. The development and introduction of these advances has manifested itself in the form of multiparametric MRI (mpMRI).

MRI machines have been commercially available since about 1982 when General Electric introduced the first whole body scanner with a magnet of 1.5 Tesla field strength. More than 20,000 of these 1.5 Tesla machines have been in daily use in hospitals and clinics in practically every country on earth. The introduction of the higher strength and higher resolution 3 Tesla systems a few years ago, together with accessories specifically suited to tumour detection and biopsy sampling are revolutionizing prostate cancer detection and quantitation. The high field strength and associated magnetic ‘gradients’ of 3T machines, allow the collection of tumour specific information for tumours as small as 0.5 ml in volume. The machine can be set up to detect high-grade clinically significant prostate cancer rather than low-grade disease that does not require active management.

It is usual for a gadolinium-based contrasting agent to be intravenously injected before the MRI session begins. The newer systems generally complete the scan in lesser time than the earlier machines which often went on for 40 to 60 minutes.

Should the scan reveal the presence of tumours, it is possible (but unlikely) for the interventional radiologist to collect biopsy samples from each tumour of size, during the MRI session. This is referred to as a direct ‘in-bore’ biopsy. Of course, non-magnetic needles are required to complete this sampling. This procedure replaces the TRUS procedure and it gives greater certainty that no significant cancerous lesion has been missed, even in hard to get to areas of the prostate.

A second procedure, called a fusion biopsy, sees the use of a device that ‘fuses’ the stored MRI image with real-time ultrasound images. This technique is rapidly increasing in popularity.

In 2014, the Wesley Hospital in Brisbane, Australia, concluded a two-year study[11] which showed that their mpMRI approach to diagnosing prostate cancer is highly effective in identifying life-threatening prostate cancer and at the same time reduces over-diagnosis of non-life-threatening prostate cancer. The study found that the use of multiparametric MRI (mpMRI):

Reduced the number of men needing prostate biopsies by 51%.

Reduced the problem of over-diagnosis of non-life-threatening disease by about 90%.

Had 92% sensitivity in diagnosing life-threatening prostate cancer. (Compared with the TRUS method for prostate cancer diagnosis which had 70% sensitivity in diagnosing life-threatening prostate cancer).

Multiparametric MRI (mpMRI) is so-called due to a host of software and accessories that substantially extend its clinical use. The following techniques are now in widespread use to help differentiate between malignant and benign tissue within the prostate:

T2-Weighted (T2W) imaging

In this mode the image contrast is weighted to demonstrate different anatomical structures or pathologies. It provides high resolution images of the anatomy of the prostate and its capsular wall.

Diffusion-weighted imaging (DW-MRI)

It determines the Brownian motion of free water within tissue. The increased cellularity and lesser extracellular spaces found in cancer lesions are detectable as regions of restricted diffusion by DW-MRI. The image obtained shows a contrast between diseased and healthy tissue. The impedance of water molecules diffusion can be quantitatively assessed using the apparent diffusion coefficient (ADC) value, and yields a different, but complementary image to DW imaging. The ADC value is automatically calculated by the system software.

Dynamic contrast enhanced MRI (DCE-MRI)

It records in real time the vascularity of tumours by the distribution of the wash-in or wash-out of the gadolinium contrasting agent between tissue and the blood pool. This allows the characterization of alterations in the microvascular environment resulting from tumour angiogenesis. Higher grade and large tumours are detected due to their tendency to have higher wash-in and wash-out rates. Lower grade smaller tumours are often not detected by DCE-MRI.

MR spectroscopy

It examines the concentration of biochemical disease markers, such as citrate, choline and creatinine, in tissues. Healthy prostate tissue has low levels of choline and high levels of citrate, whereas cancerous prostate tissue displays the converse, i.e. high choline and low citrate levels. This modality variant is now being used less often in prostate cancer due to time, cost and the skills needed.

Access more information on mpMRI via Appendix 3. Alternatively, review the paper titled Advancements in MR Imaging of the Prostate: From Diagnosis to Interventions by David Bonekamp, et al., published in the journal RadioGraphics.[12]

The results of the PRECISION (PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not?) study reported at the EAU18 Annual Meeting were considered to be ‘game changing’ by delegates. In this multi-centre international study, 500 men with a suspicion of prostate cancer were randomised to receive a standard of care 12 core TRUS biopsy, or an MRI directed pathway. In the MRI pathway, all patients had an MRI, and if the MRI was abnormal (72% of men), they had a targeted biopsy of the lesion(s) (with no systematic biopsy; i.e. only the abnormal lesion was biopsied). If the MRI was normal (28% of men), they did not have a biopsy, and continued on routine PSA surveillance. The primary outcome was detection rate of clinically significant cancer; and secondary outcomes included the detection rate of clinically insignificant cancer. In the standard of care arm, the detection rate of clinically significant cancer was 26%, and the detection rate of clinically insignificant cancer was 22%. In the MRI pathway, the detection rate of clinically significant cancer was 38%, and the detection rate of taking insignificant cancer was 9%. The authors suggested that these findings should provoke an immediate change in the diagnostic pathway for early prostate cancer in two ways:

Firstly, all patients with a clinical suspicion of prostate cancer should be offered an MRI as part of their informed/shared decision-making pathway, and all patients with an abnormal result on their MRI scan should be offered a targeted biopsy alone.

The obvious concern of course, is the fate of those patients with a normal MRI (28% of patients), who despite a clinical suspicion of prostate cancer, did not have a biopsy. How many clinically significant cancers might be missed by not offering a biopsy to those patients? They concluded that these men should be placed on active surveillance, with specific PSA targets that would ‘trigger’ a targeted biopsy.[18]

So, what is clinically significant prostate cancer? The best definition I have seen is: Prostate cancer which has a high likelihood of progressing, metastasizing and/or causing mortality within the lifespan of the patient. In other words, it is disease that adversely impacts quality of life and longevity and demands immediate treatment. In contrast, insignificant cancers are suited for active surveillance with treatment deferred until the cancer progresses.

As we have read earlier, prostate cancer is diagnosed by a pathologist histologically examining biopsy samples that have been (mainly) obtained using a transrectal ultrasonic-guided device. Sampling error could cause cancerous growths to be missed and indolent cancers are often over-detected leading to unnecessary clinical intervention. The recent introduction of more powerful (and thus higher resolution) MRI systems has seen mpMRI come to the fore as a prostate cancer diagnostic tool. [13]

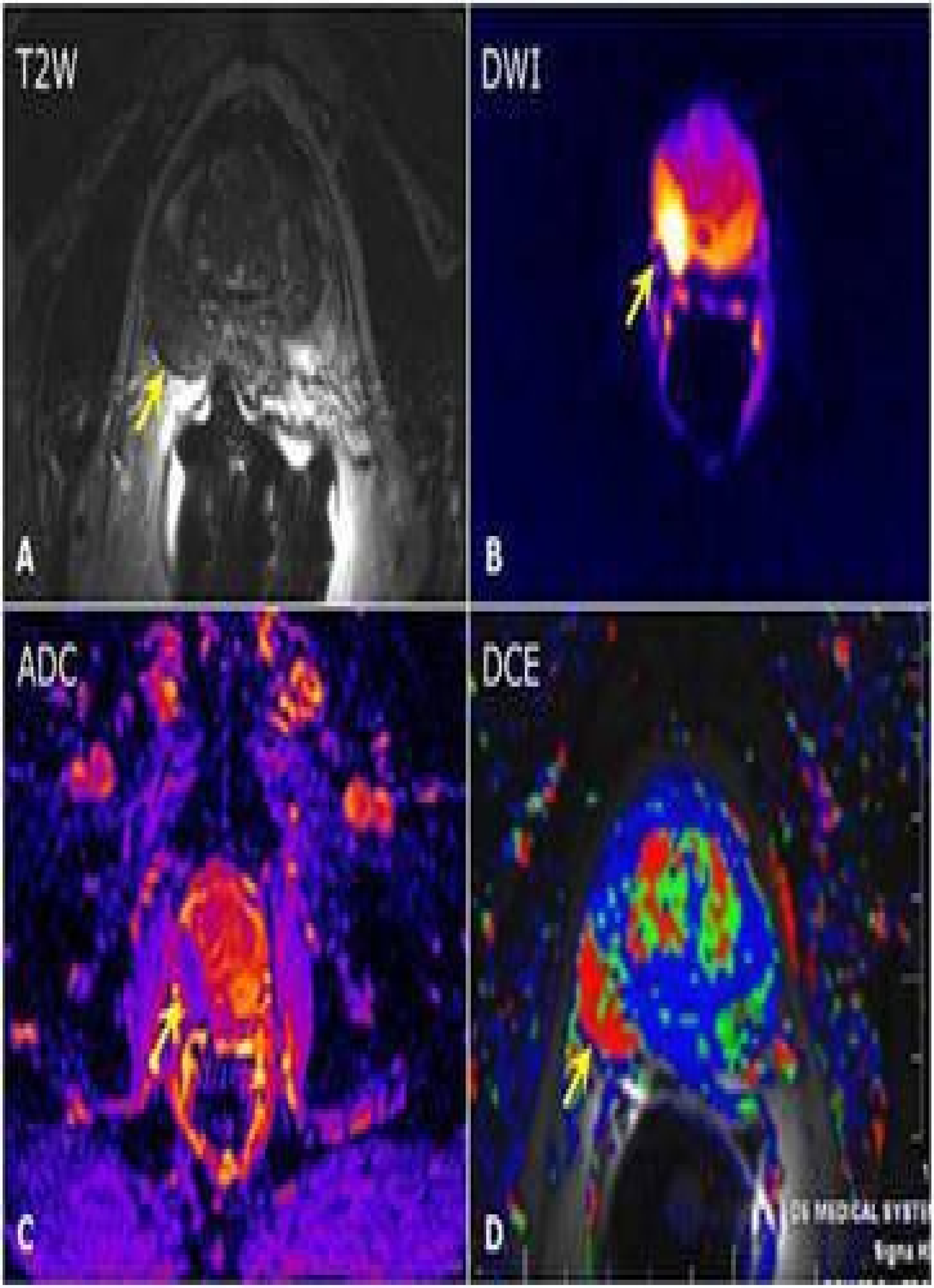

T2W
DWI
A
B
ADC
DCE
C
D
GE MEDICAL SYSTE
Signa H

Image: Courtesy of Radiology Rounds Vol. 8, Issue 8, 2010 newsletter

The Axial Multiparametric MR Images above are: A) T2-weighted, B) diffusion weighted (DWI), C) apparent diffusion coefficient (ADC) and D) dynamic contrast enhanced (DCE) images of a patient with prostate cancer. The tumour appears dark on the axial T2-weighted image (arrow); the corresponding area shows restricted diffusion on the DWI and ADC images as well as abnormal contrast enhancement on the DCE axial image (as evident from abnormal red colour coding of the tumour).

A new prostate-imaging technology that fuses MRI with real-time three-dimensional ultrasound may offer a more exacting method to obtain biopsy specimens from suspicious areas within the organ. This 2011 development at UCLA combines the use of an MRI with advanced Doppler ultrasound technology to produce a 3D ‘fusion’ image that is used to accurately target ‘suspicious’ areas of the prostate. The MRI-ultrasound fusion technique is best suited to those who have had prior negative biopsies, but have persistently elevated PSA levels, and for ‘active surveillance’ patients (those with low-risk prostate cancers, who are being carefully monitored over time to see if their cancer progresses or becomes more aggressive). The UCLA team found that targeted biopsy was about five times more likely to find cancer than non-targeted, systematic biopsy. More details and a video on the technique are accessed via Appendix 3.

The use of an endorectal coil (ERC) provides higher accuracy than other modalities in assessing seminal vesicle invasion and extra-capsular extension (ECE) of prostate cancer (96% and 81% respectively). Another study found the ERC provided an overall sensitivity and specificity for ECE of 75 % and 92 %, respectively.[14]

The importance of mpMRI as a diagnostic tool for prostate cancer was emphasised in early 2012 when the European Society of Urogenital Radiology introduced their ESUR prostate MR Guidelines.[15] These clinical guidelines for the multi-parametric MRI of the prostate were prepared by a group of prostate MRI experts from the ESUR, and are based on literature evidence and consensus expert opinion. The guidelines outline the optimal technique recommended for prostate cancer diagnosis and include three protocols for the ‘detection’ of prostate cancer, the ‘staging’ of the disease and, in the case of metastatic cancer, the ‘node and bone’ progression of the disease. They also cover the use of an endorectal coil to improve signal to noise ratios (resolution) and compare the endorectal coil verses the alternative non-invasive pelvic phased-array coil. It also reviews the difference in performance of the earlier 1.5 Tesla systems verses the more sensitive 3 T machines.

In 2012, the European Society of Urogenital Radiology (ESUR) introduced new guidelines including a new scoring system, called the PI-RADS classification system which was designed to enable uniform structured reporting of prostate cancer mpMRI results. PI-RADS is an abbreviation for Prostate Imaging Reporting and Data System and is broadly based on the breast cancer scoring system, BI-RADS. With the rapid advancement of mpMRI internationally, an updated version called PI-RADS V2, was introduced in 2015. These new guidelines are being taken up by radiologists worldwide.

The PI-RADS score is for men who have not yet undergone treatment. The scores are:

PI-RADS 1: very low – clinically significant cancer is highly unlikely to be present.

PI-RADS 2: low – clinically significant cancer is unlikely to be present.

PI-RADS 3: intermediate –the chance of clinically significant cancer is neutral.

PI-RADS 4: high – clinically significant cancer is likely to be present.

PI-RADS 5: very high – clinically significant cancer is highly likely to be present.

PI-RADS assists in the ‘standardisation’ of result reporting in these instances. It also provides scoring that can be linked back to the universal Gleason scoring system.

Not all MRI facilities had previously used all three of TW2, DW, and DCE, with even fewer using the Spectroscopy capability. The ongoing development of MRI machines to include wide-bore machines, has seen an increase in the number of in-gantry MRI-guided biopsies (referred to as MRGBs) being done. Removal of the cancerous lesion/s by HIFU or FLA whilst the patient is within the wide-bore MRI machines is also occurring.

The time to complete a mpMRI scan obviously impacts its price. Lower cost and quicker variants are now being done with very little, if any, difference in results. The currently-used mpMRI versus non-contrast bpMRI in three planes (bpMRI) and in one plane (‘fast’ bpMRI) to detect high-grade prostate cancer are completed in 30-45 minutes versus 13 and 8 minutes respectively, also without the use of an invasive contrasting agent.

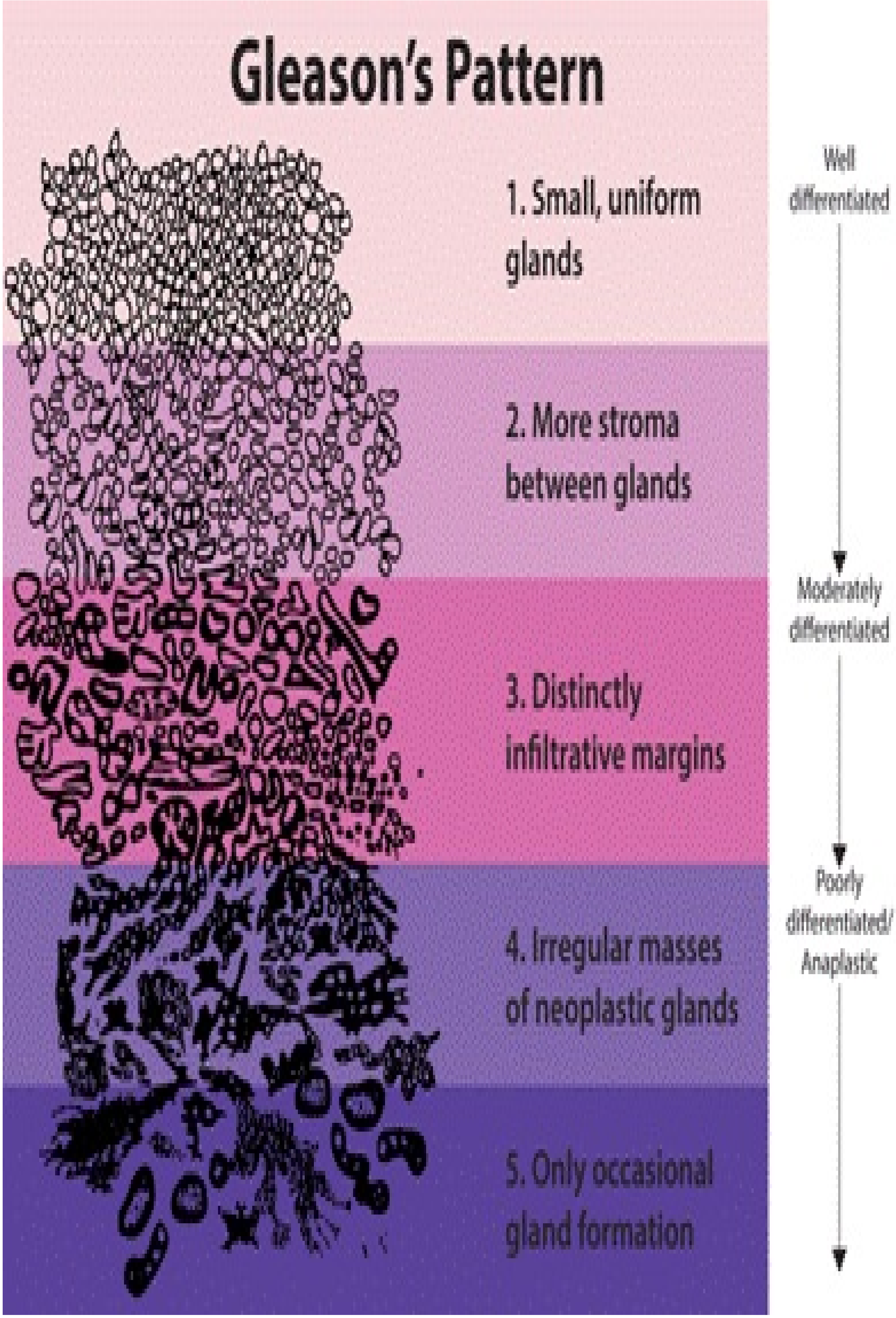
Staging - A Positive Biopsy Result

The tissue removed during the biopsy is examined by a pathologist under the microscope to look for abnormal or cancerous cells in the tissue. If cancer cells are present the pathologist will grade the tumour/s against an internationally accepted scale for grading prostate cancer, called the Gleason Score.

Gleason scores range from 2 to 10. Tumours with higher grades tend to grow faster than those with lower grades and they are also more likely to spread. Doctors use tumour grade along with your age and other factors to suggest treatment options. To determine the Gleason score, the pathologist examines the patterns of cells in the prostate tissue samples. The most common pattern of cells is given a grade of 1 - this being most like normal prostate tissue - to grade 5 (most abnormal). The pathologist gives the second most common pattern a grade of 1 to 5 and then adds the grades for the two most common patterns together to make the Gleason score (3 + 4 = 7). If only one pattern is seen, the pathologist counts it twice (5 + 5 = 10). Gleason grades of 6 or less suggest a low risk from the cancer. A score of 7 suggests moderately differentiated cells and an intermediate risk. Scores of 8 to 10 suggest high risk to the patient. A high Gleason score (such as 10) means a high-grade prostate tumour. See image on the next page.

If a patient is confirmed with prostate cancer, the lowest Gleason available is Grade 6 (3 + 3) or ISUP Grade Group 1. This suggests the tumour is slow growing and that the patient is likely to be a candidate for active surveillance. Higher grades call for more aggressive therapies.

In 2014, the World Health Organisation recommended that all health authorities replace the Gleason score with the simpler ISUP Grade Group system. Many health jurisdictions rapidly adopted the new system, but others have been slow to take up the new system. Some still report both scores.



Gleason's Pattern

1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation
Well differentiated
Moderately differentiated
Poorly differentiated/ Anaplastic

Image: SEER Training Modules, Prostate Cancer. U. S. National Institutes of Health, National Cancer Institute. 1st February. 2015 http://training.seer.cancer.gov/prostate/abstract-code stage/morphology.html/>.

ISUP Grade Group versus Gleason Score Comparison

Risk Group	ISUP Grade Group	Gleason Score
Low	Grade Group 1	Gleason Score 6
Intermediate Favourable	Grade Group 2	Gleason Score 7 (3+4)
Intermediate Unfavourable	Grade Group 3	Gleason Score 7 (4+3)
High	Grade Group 4	Gleason Score 8
High	Grade Group 5	Gleason Score 9 - 10

Staging – TNM Score

Doctors also provide a different score which records how far the cancer has spread. The TNM Score is used around the world to stage cancers which develop as tumours and metastasise elsewhere in the body. The letters T, N and M refer to different locations of the cancer. (In the United States, a different system is partially still in use which uses Roman numerals. A Stage I cancer is early stage cancer whereas a Stage IV cancer has spread to other parts of the body).

The T score is the rating and size of the primary tumour. T1 tumours cannot be felt by DRE or by imaging. Cancer is on occasion found in biopsy samples taken when a patient undergoes a surgical procedure for an enlarged prostrate. This phenomenon is often referred to as an incidental finding. In these occurrences, the T1 score is further recorded as T1a, T1b or T1c with T1a and T1b referring to the incidental findings. T1c tumours are ones found by needle biopsy.

T2 tumours can be felt by doctors during DRE. They also may be seen with an imaging test. T2 tumours are those that haven’t grown outside the prostate and are based on cancer growth within the left or right lobes of the prostate. T2a tumours haven’t grown beyond half of one lobe. T2b have grown beyond half of one lobe. T2c tumours have grown in both lobes.

T3 tumours have grown outside the prostate. They have reached the seminal vesicles, the neck of the bladder, or the connective tissue around the prostate. Imaging tests are used to locate T3 and T4 tumours. T4 tumours have spread to tissue near the prostate including the external sphincter, rectum, bladder levator muscles and pelvic wall.

Staging – Nodes

The N category indicates if the cancer has spread to the nearby lymph nodes. Imaging tests determine these values. N0 means that the cancer has not spread to the lymph nodes. N1 means it has spread into the nearby lymphatic system. NX means it is unknown if the cancer has reached the lymph nodes.

Staging – Metastasis

The M score indicates that the cancer has spread to distant body sites which include other lymph nodes, the bones or liver. It is only determined after at least two imaging tests. M scores for prostate cancer include:

MX – unknown if cancer has spread to distant sites

M0 – no growth in distant sites

M1 – cancer has spread to distant sites

M1a – cancer that has spread to lymph nodes

M1b – cancer that has spread to bones

M1c – cancer that has spread to distant organs.

Imaging Tests

Before the doctors determine a course of action to treat localised or advanced prostate cancer, it is necessary for the patient to undergo a Bone Scan and a CT Scan (or an MRI Scan instead of the CT Scan). These tests are done to determine whether or not, the cancer has spread to the lymph nodes, the seminal vesicles, other organs or the bones (metastasis).

In cases of recurrent prostate cancer and/or suspected of metastatic prostate cancer, the urologist may order a Choline, Axumin or PMSA PET/CT Scan which give higher resolution images. (See the next chapter on Imaging).

Colour Doppler Ultrasound

We learnt earlier that a transrectal ultrasound (TRUS) is a non-invasive procedure in which an ultrasonic probe is inserted into the rectum in order to take an image of the prostate. It works by using a technique called the Doppler Effect. It allows the doctor to ‘see’ the prostate and accurately determine its volume and dimensions. The volume of the prostate is used to calculate a predicted PSA value. This value is compared with the patient’s actual PSA value with higher actual values signalling further possible testing and intervention. Men with very large prostates usually have a higher ‘normal’ PSA value than those with prostates that are of average size.

It is also used in the biopsy procedure. Most urologists use systems that provide black and white images only. In recent years, the Colour Doppler Ultrasound system has been favoured over the black and white version, as it offers higher resolution, greater precision and includes tissue harmonic technology. There is also another higher sensitivity version of the Colour Doppler which is the Power Colour Doppler Ultrasound. The Power Doppler is often referred to as the Energy Doppler, as it operates by measuring the power (energy) of the many different frequency shifts inside each measurement cell, which are added to form the power signal. The very latest Colour Doppler machines offer sensitivities similar to or even better than the Power Doppler Ultrasound machines.

The most important consideration for using a Colour Doppler TRUS, is its ability to more accurately detect small abnormalities within the prostate by observing its blood flow patterns. If higher blood flows are detected, it is likely that the indicated areas are cancerous, due to neovascularity (abundance of blood vessels inside the tumour). In cases where the PSA level is higher than the predicted level and anomalous areas are detected, it would be appropriate for a biopsy to be undertaken. The absence of these two factors would suggest a follow up PSA down the track and a watchful waiting stance be adopted.

The recently-developed Tissue Harmonic technology, referred to above, improves spatial resolution of the system to permit visualization of smaller objects and improves contrast resolution to provide very subtle differences in the grayscale of the Doppler image. The technique of using Tissue Harmonic technology with Colour Doppler TRUS practiced by Dr Duke Bahn of the Prostate Institute of America, also evaluates the likelihood of the prostate cancer being fully confined to the prostate or otherwise. Access full details of his procedure via Appendix 3. Power and Colour Doppler Ultrasound are very important tools in the pre-diagnosis of prostate cancer before biopsy. Together with mpMRI, these techniques are likely to lead to fewer unnecessary biopsies being undertaken and random biopsies being passed into history in favour of the targeted biopsy. In coming years, it should become common practice for men with elevated PSA levels to undergo both these procedures before a biopsy is recommended.

Too Many Biopsies?

Health administrations in most countries are acutely aware of the high cost of conducting biopsies, particularly in light of the high negative rate. Research is being funded to try to reduce the ‘over-servicing’ of possible prostate cancer sufferers. A research group led by Dr Henrik Grönberg, from the Karolinska Institute in Stockholm, Sweden, recently reported that their multi-parameter Stockholm 3 (STHLM3) prostate cancer screening algorithm test can significantly reduce the rate of unnecessary biopsies without compromising the identification of high-risk prostate cancer, when compared against current practice.

The STHLM3 algorithm includes a combination of plasma protein biomarkers (some being PSA, free PSA, intact PSA, and human kallikrein 2) and clinical variables such as age, family history, previous prostate biopsy, and prostate examination results. These results were found to reduce the need for biopsies in benign or low-risk cases by 55%. This test is likely to be commercialised and gain widespread acceptance in coming years. Thus, its inclusion in this book.

Patient Indices

The completion of questionnaires by patients assists urologists in their pre- and post-treatment options. These include some or all of the following indices or scores:

The International Prostate Symptom Score (IPSS), International Index of Erectile Function-15 (IIEF-15), UCLA-Expanded Prostate Cancer Index Composite (EPIC), and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) score.

The International Prostate Symptom Score (IPSS) is an 8 question (7 symptom questions + 1 quality of life question) in the form of a questionnaire, with the answers used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of the disease benign prostatic hyperplasia (BPH). The IPSS is designed for easy completion by the patient and assists the medical practitioner in formulating treatment for the condition. It was designed by the American Urological Association in the 90's and it originally lacked the 8th quality of life question, hence its original name: the American Urological Association symptom score (AUA-7).

International Index of Erectile Function-15 (IIEF-15) is a brief 15-item, self-administered questionnaire that was developed as a measure to detect treatment-related erectile function in patients in cross-cultural settings. Relevant cross-cultural domains of sexual function were identified via the literature and were reviewed and endorsed by an international panel of experts. These include: Erectile Function (6 items), Orgasmic Function (2 items), Sexual Desire (2 items), Intercourse Satisfaction (3 items) and Overall Satisfaction (2 items). The 15 questions are answered by the patient against provided criteria with the results of considerable use to the urologist.

Expanded Prostate Cancer Index Composite (EPIC) is a questionnaire that requests the patient to quantify against provided criteria, levels of urinary function, bowel activities, sexual function and overall satisfaction post treatment.

Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a multidimensional, self-report Quality of Life questionnaire specifically designed for use with prostate cancer patients. It consists of 27 core items which assess patient function in four areas: Physical, Social/Family, Emotional, and Functional well-being, and is further supplemented by 12

site specific items to assess for prostate related symptoms.

The PCPT Prostate Cancer Risk Calculator was the first on-line prostate cancer risk assessment tool to allow men to assess their own risk for prostate cancer. This calculator emerged from the Prostate Cancer Prevention Trial (PCPT) in the USA. Obviously, the results obtained should always be discussed with your doctor. The tool developed in 2006 by Thompson, et al., is based on data developed from 5,519 men in the placebo group of the PCPT trial. It only included men who went on to have a biopsy after the completion of the therapy stage of the trial. The tool was upgraded in 2012 after further patient data became available from the PCPT trial. This improved calculator is referred to as the PCPTRC 2.0. It is accessible via Appendix 3. Their nomogram is based on: PSA result, DRE findings, any prior biopsy data, age, family history of prostate cancer, and ethnicity. It is still considered to be the nomogram for assessment of the risk for prostate cancer, even though newer nomograms, such as the Sunnybrook nomogram, which assess additional data, have arrived on the scene.

Let’s look at an example using my data (as of early 2012):

Age: 67 years

PSA level: 7.5 ng/ml

Ethnic background: Caucasian

Family history of prostate cancer: Yes (Father and Brother)

Positive or negative DRE result: Negative

Prior negative prostate biopsy: None

With this data inserted into the PCPT calculator, the results are:

Est. risk of biopsy-detectable high-risk prostate cancer: 13 %

Est. risk of biopsy-detectable low-risk prostate cancer: 26 %

Probability of a negative biopsy result (i.e., no evidence of prostate cancer): 61 %

Chance that he will have an infection that may require hospitalization: 2 to 4 %.

Clearly, the results from the calculator can only be considered a guide and the results obtained must be discussed with your doctor. Let's put my actual results into perspective against the above results:

Diagnosed with intermediate prostate cancer with a Gleason Score of 3+4 = 7

Nine out of 24 biopsy cores were positive for cancer.

The University of Texas Health System Centre web site also includes an updated version of the calculator that allows any PCA3 test data to be added if you have had this test.

The Sunnybrook Prostate Cancer Risk Calculator uses the same criteria as the PCPTRC 2.0 calculator plus the patient’s urinary symptoms (measured by the International Prostate Symptom Score index) and the Free to Total PSA ratio value. Unfortunately, I don’t have the results of these two values available and as such cannot compare the two calculator results. The Sunnybrook calculator is accessible via Appendix 3. (Sunnybrook Health Sciences Centre, Toronto, Canada). Both hospital web sites include a video on the use of their calculator as well as requiring persons wanting to use the calculators to acknowledge a disclaimer before accessing the calculator.

The SWOP Prostate Cancer Research Foundation in Oostvoorne in association with the European Randomized Study of Screening for Prostate Cancer (ERSPC), lists seven risk calculators. These are accessible via Appendix 3.

Memorial Sloan Kettering Cancer Centre have developed their own nomograms for pre-radical prostatectomy, post-radical prostatectomy, salvage radiation therapy and the risk of dying of prostate cancer if their cancer recurs, signalled by a rising PSA, after radical prostatectomy. These are accessible via Appendix 3.

Prognostic Nomograms

The Kattan nomograms predict recurrence after surgery and/or radiation therapy, based on data available either at the time of diagnosis or after surgery. The nomograms can be calculated using paper graphs or software available on a website or for hand-held computers. The Kattan score represents the likelihood of remaining free of disease at a given time interval following treatment.

The Partin tables are the best nomogram for predicting prostate cancer spread prior to therapy. The look-up tables were updated by experts at Johns Hopkins in 2013. The updated tables show that certain categories of men who were previously not thought to have a good prognosis (e.g., those with a Gleason score of 8) actually can be cured with surgery.

The D'Amico classification stratifies men by low, intermediate, or high risk based on stage, grade, and PSA. It was used widely in clinical practice and research settings, but less so now.

The UCSF Cancer of the Prostate Risk Assessment (CAPRA) score predicts both pathologic status and recurrence after surgery. It offers comparable accuracy as the Kattan pre-operative nomogram and can be calculated without paper tables or a calculator. Points are assigned based on PSA, grade, stage, age, and percentage of cores positive; the sum yields a 0 to 10 score, with every 2 points representing roughly a doubling of risk of recurrence. It has been validated among over 10,000 prostatectomy patients and has been shown to predict metastasis and mortality following prostatectomy, radiation therapy, watchful waiting, or androgen deprivation therapy.

The Prostate Cancer Risk Index (PRIX) nomogram has been developed to predict those men who will undergo treatment failure after a prostatectomy. It should enter general practice in 2020. The PRIX score is calculated from the total serum PSA pre-surgery, the biopsy Gleason score and clinical stage. Circulating prostate cells are detected from venous blood one month after surgery, by standard immune-cytochemistry. A test is considered positive when one circulating prostate cell is detected. Patients were followed up for five years and biochemical failure was defined as a serum PSA >0.2 ng/ml.

Metastatic Cancer

As distressing as it is, many prostate cancer sufferers will see their disease progress to the point that it metastasises into the bones, lymph nodes, and organs such as the lungs and liver.

Present conventional treatments are extending the quality of life of sufferers and longevity itself. More and more research outcomes from completed clinical trials are leading to better and better treatments being introduced on a regular basis. Many sufferers are confounding the doctors by progressing better than expected. Some achieve permanent regression of their cancer.

Researchers at the Duke Cancer Institute and other top cancer centres have found that the organ site where prostate cancer spreads has a direct impact on survival.

Patients with lymph-only metastasis have the longest overall survival, while those with liver involvement fare worst. Lung and bone metastasis fall in the middle. These findings were reported in a study published online on 7th March 2016 in the *Journal of Clinical Oncology*. All 8736 men had participated in one of nine large, phase III clinical trials for men with metastatic prostate cancer. The patients had all undergone standard treatment with the chemotherapy drug docetaxel.

Median survival rates were: Lymph nodes – 32 months; Bones – 21 months; Lungs – 19 months; Liver – 14 months.

Of course, newer drugs are keeping the disease at bay and other gains are being made. See Chapter 15 for more on metastatic cancer.

Chapter 4.

Imaging

After a positive biopsy, the medical team must develop a plan of action to treat the cancer, but first it must be determined if it is localised or advanced prostate cancer. To do this, it is necessary for the patient to undergo a Bone Scan and a CT Scan (or an MRI Scan instead of the CT Scan). These tests are done to determine whether or not, the cancer is still contained with the prostatic capsule or has spread to the lymph nodes, the seminal vesicles, other organs or the bones (metastasis).

Many men experience a return of their prostate cancer after being in remission for periods of 2 to 10 years or more. In these cases, and/or suspicion of metastatic prostate cancer, the urologist may order a Choline, Axumin or PMSA PET/CT Scan which give higher resolution images.

Bone Scan

The purpose of the bone scan is to see if the cancer has spread to the bones. A small amount of low dose radioactive material (usually technetium) is injected in an arm vein. The test, which requires the patient to lie still on a padded table for about 40 minutes, is started about two hours after the technetium is injected. The padded table is introduced below a special (gamma) camera that ‘sees’ the radioactive material. Prostate cancer, reaching the pelvic bone or spine, causes damage to the bones. The efforts of the bone to repair itself attract the radioactive material and these areas appear as ‘hot spots’ on the bone scan.

Other medical conditions can also lead to the concentration of the radioactive material in the areas of bone repair. The radiologist is proficient in determining what prostate cancer is and what is not. Of course, if the cancer has only just migrated to the bones, insufficient cancer cells may be present to have caused bone damage. A bone scan is rarely positive when the PSA level is less than 20 ng/ml. If the bone scan determines that the cancer has spread to the bones, it will be necessary for the patient to undertake treatments that target whole body cancer.

Test results are usually only available about 48 hours after the test is completed. Patients undergoing a bone scan can resume normal activities after the scan has been completed. (Some patients are given a sedative before the scan to assist them to remain still whilst undertaking the approximately 40-minute test. This sedative needs to wear off before normal activities, like driving a car, are resumed).

CT Scan

A CT or CAT scan refers to a computerised tomography scan, is a simple and routine test that takes up to an hour. A CT scan uses x-rays to present the radiologist with a 3-dimensional view of the body and its organs section by section. Dye is injected into an arm vein and the patient also drinks a fluid that helps contrast images of the pelvic area. The purpose of the CT scan is to provide information of the possible spread of the cancer to the lymph nodes in the pelvic area. It also provides very accurate measurement of the size and precise position of the prostate relative to the surrounding organs. These measurements are very important for the planning of any external beam radiation that might follow these imaging tests.

PET Scan

A PET scan uses Positive Emission Tomography to picture images of any anomalies such as tumours in the body. A radiologist injects a small amount of radioactive material (called a tracer) into the patient. This tracer is bound to a ligand (now called a radioligand) that searches out receptors on the surface of cancer cells. The system detects pairs of gamma rays emitted indirectly by the positron-emitting radioligand, historically most commonly fluorine-18, but more recently gallium-68. Different ligands are used for different imaging purposes, depending on what the radiologist/researcher wants to detect. 3D images of the tracer accumulation within the body are then constructed by computer analysis. In modern PET-CT (computed tomography) scanners, 3D imaging is achieved with the aid of a computed tomography X-ray scan performed simultaneously on the patient during the same session. A word of caution: PET-CT scans expose the patient to significant amounts of ionizing radiation from both the PET tracers and the simultaneous CT scan. It is not something one would do too often. Doctors commonly refer to a PET scan, when they mean a combined CT scan with a PET overlay. This combined technique yields more information than either technique alone. PET-CT scans assist in identifying precise further biopsy targets; in development of a radiation plan and determining the progress of any cancer treatment. It is often referred to as functional imaging.

How accurate are these various technologies? One way to look at it is to determine what level of PSA can be detected by the various modalities. A C-11 Choline PET-CT is considered able to reliably detect metastases when the PSA is around 2 ng/ml, rather than 20 ng/ml for a bone scan. (The senior urologist that reviewed this text advised that Choline PET-CT is no longer in use in a clinical setting in Australia due to the very short tracer half-life). The newer PSMA PET-CTs are many times more sensitive in detecting even earlier metastases, at around the 0.5 ng/ml level.

PSMA PET Scans

Prostate-specific membrane antigen (PSMA) positron emission tomography

(PET) imaging has become a popular method for determining the location of any prostate cancer and in some cases, the stage of a patient's prostate cancer. As noted above, it offers extremely high-resolution images of cancer lesions in the bones and in soft body tissue.

Nepean Urology Research Group, Nepean Hospital near Sydney, Australia, in June 18 reported their findings of a chart review of 50 male patients staged for prostate cancer using PSMA PET-CT versus mpMRI who then underwent radical prostatectomy. A total of 81 lesions were confirmed by histopathology. Fifty index lesions were detected by histopathology, all of which were detected by PSMA PET-CT (100% detection), and 47 by mpMRI (94% detection). Thirty-one histologically confirmed secondary lesions were detected, 29 of which were detected by PSMA PET-CT (93.5% detection), and 16 by mpMRI (51.6% detection). PSMA had better sensitivity for index lesion localization than mpMRI (81.1 vs. 64.8%). Specificity was similar for PSMA PET-CT and mpMRI (84.6 vs. 82.7%).

The research group concluded that the PSMA PET-CT provided superior detection of prostate cancer lesions with better sensitivity than mpMRI and that the PSMA PET-CT can be used to enhance loco-regional mpMRI to provide improved detection and characterization of lesions. See Appendix 3 for more details.

Also, in June 18, a study reported on the detection rate of PET-CT scans using tracers ^{68}Ga-PSMA versus ^{11}C-Choline in men with prostate cancer with biochemical recurrence and to demonstrate the added value of a tri-modality PET-CT-MRI system. Thirty-six men underwent both scans. In addition, to the ^{68}Ga-PSMA scan, a PET-CT-MRI (3 Tesla strength) system with a dedicated shuttle, acquired MRI images of the pelvic region.

Both scans were positive in 18 patients (50%) and negative in 8 patients (22%). Nine patients were positive with ^{68}Ga-PSMA alone (25%) and one with ^{11}C-

Choline only (3%). The median detected lesion per patient was 2 for ^{68}Ga-PSMA (range 0-93) and 1 for ^{11}C-Choline (range 0-57). The number of lesions detected with the ^{11}C-Choline tracer was PSA level dependant whereas for ^{68}Ga-PSMA the number of detected lesions was independent of PSA levels. Metastatic pelvic lesions were found in 25 patients (69%) with ^{68}Ga-PSMA PET-CT, in 18 (50%) with ^{11}C-Choline PET-CT and in 21 (58%) with MRI. Some recurrences were found to be indeterminate by means of PET-CT alone. The study found that MRI was very useful in detecting recurrence in the prostate bed.

In summary, ^{68}Ga-PSMA detected more lesions per patient than ^{11}C-Choline, regardless of PSA levels and that a PET-CT-MRI (3T) system added increased accuracy of diagnosis.

Another study compared the performance of ^{68}Ga-PSMA PET, ^{18}F-NaF PET-CT (often referred to as FDG PET) and diffusion-weighted MRI (DW600-MRI) in prostate cancer patients with BCR. ^{68}Ga-PSMA-PET and ^{18}F-NaF PET-CT showed comparable and high diagnostic accuracies for detecting bone metastases in men with BCR. Both methods performed significantly better than DW600-MRI, which was inadequate for diagnosing bone metastases when conducted in accordance with European Society of Urogenital Radiology guidelines.

In a systematic review and meta-analysis paper in the February 19 European Urology, M. Perera et al., reported on their analysis of 37 articles including 4790 patients. The review found that significant differences in positivity after BCR in the prostate bed were noted between radical prostatectomy (22%) and radiotherapy (52%) patients. An informative statistic. ^{68}Ga-PSMA-PET improves detection of metastases with BCR, particularly at low pre-PET PSA levels of >0.2 ng/ml and 0.2 - 0.5 ng/ml. ^{68}Ga-PSMA-PET produces favourable sensitivity and specificity profiles on meta-analysis of pooled data.

A large number of research groups are working on PSMA Pet tracers. Research shows that one such tracer - ^{18}F-rhPSMA PET had more favourable parameters in diagnosing N-staging of prostate cancer compared to the commonly used ^{68}Ga-PSMA-PET. It demonstrated the increased sensitivity (72.2%), specificity (92.5%), and accuracy (86.2%) of ^{18}F-rhPSMA PET compared to the morphological (CT) imaging (50.0%, 72.5% and 65.5%).

Magnetic Resonance Imaging (MRI)

MRI machines use a powerful magnetic field to produce pictures of the internal organs, bone and soft body tissue to again determine if the cancer has spread outside of the prostate. A MRI is a more claustrophobic and noisy test than a CT scan. Patients are required to remove all metallic objects such as watches and jewellery before undergoing a MRI. Some metallic implants prevent the use of an MRI. The MRI images produced also assist in planning for future prostate surgery.

It is possible that the CT or MRI scan (or a PSMA PET scan) will detect the spread of the cancer to the lymph nodes near the prostate gland. In these cases, it is likely that the patient will be required to pay a return visit for a further CT, MRI or PSMA PET scan, during which a fine needle aspiration procedure will be undertaken under local anaesthetic. This procedure provides a biopsy sample from the lymph nodes for pathological analysis.

Some earlier MRI machines were of lower resolution having a 1.5 Tesla strength magnet. On occasion the radiologist might use an extension to the 1.5T, or even the 3T machine, called an endorectal coil. The coil is placed into the rectum in order to obtain the high-quality images of the area surrounding the rectum. The technique yields higher accuracy than other methods in determining seminal vesicle invasion and extra-capsular extension of the prostate cancer. The coil consists of a probe with an inflatable balloon which helps maintain appropriate positioning.

In the March 19 issue of The Journal of Urology, a study reported that a 3T mpMRI with and without an endorectal coil yielded similar detection of overall and index prostate cancer. Interestingly, the endorectal coil sub-group had significantly higher detection of posterior and peripheral prostate cancer, and lower detection of anterior and transition zone prostate cancer. Remember that 70% of prostate cancers start in the peripheral zone.

Since 2015, the European Association of Urology (EAU) recommended that every repeated prostate biopsy should be carried out based on a mpMRI examination and any abnormalities found in it. From 2019, the EAU also recommended that every patient who is booked for a prostate biopsy should undergo a prostate MRI first. MRI is performed specifically for the purpose of a subsequent prostate fusion biopsy.

PART 2: TREATMENT OPTIONS

Chapter 5.

Introductory Comments on Treatment Options

So, you are diagnosed with prostate cancer. The urologist will discuss in detail the nature of your disease, the treatment options available to you, and how the treatment options might match your priorities. Sometimes the most aggressive and effective treatment causes side effects that the patient might not be able to accept or cope with. You will be informed of the extent of your prostate cancer (stage) and the rate at which it is growing (grade).

It is a good idea to have your wife or other confidant, also attend this interview with the specialist, as it is very difficult for the patient to remain psychologically composed enough to taken in all the information imparted by the specialist. It is also appropriate to make a list of questions to ask the specialist and take the list with you to the appointment. Don’t be embarrassed by the nature of your questions. Remember it’s the specialist’s responsibility to fully inform you as to your condition, the threat it might pose to your health, the possible treatment options and the relevant side effects. Also bear in mind that prostate cancer is generally a slow progression disease. It is thus appropriate that time be taken to make a decision on the most appropriate treatment for you. This is likely to require you to make a return visit to your specialist some days or weeks after you have been informed of your PC diagnosis. This is particularly relevant for men diagnosed with localised prostate cancer. It is likely that the specialist will provide you with hard-copy material of treatment options, side effects etc. when you are informed that you have prostate cancer. Study these carefully to get a better understanding of the treatment options, side effects, and risks to your health, etc.

It is likely that the specialist will also discuss with you the impact of your age, and other health conditions that you might have, on the treatment proposed. Life expectancy, of say, a 55-year-old male is quite different to an 80-year-old man who might have other serious health conditions which suggest a life expectancy of less than the average life expectancy of around 82 years. The doctor may refer to nomograms, which are prediction tools that can be used to decide which treatment approaches will result in the greatest benefit for men at various stages of prostate cancer.

A pre-treatment (post-biopsy) nomogram can be used to predict the probability of cancer remaining progression-free, following radical prostatectomy or brachytherapy. The nomogram lists the latest patient data versus the doctor's or hospital's standard criteria:

Most recent PSA (prostate-specific antigen) value.

Primary and secondary Gleason grade.

Doctor's assessment of patient's clinical tumour stage (TNM details).

Number of positive cores (samples) found during biopsy.

Number of negative cores (samples) found during biopsy.

Planned radiation therapy dose if patient has already seen a radiation oncologist.

Whether patient has had previous hormone treatment.

Whether patient has had radiation treatment.

Jani and Hellman in 2003 reported (Lancet 361 1045-1053) the increasing complication rates for early stage prostate cancer suffers are as shown in the table below.[1] (Whilst this paper is somewhat dated, today's results are not greatly dissimilar to those below).

Issue	Prostatectomy	EBRT	Brachytherapy	Brachytherapy with EBRT
Rectal	+	+++	+	++
Impotence	+++	++	+	++
Incontinence	+++	+	+	+
Urine Retention	+	+	+++	+++

Increasing number of +s indicates increasing complication rates.

Daniel A. Barocas, MD, (Vanderbilt University Medical Centre) et al., authored a comprehensive report of side effects that men experienced, over 36 months post therapy, after radiation therapy, radical prostatectomy, hormone therapy or active surveillance.[2] See Appendix 4 to access the paper.

The following are the ten main treatment options, some of which have different sub-sets that provide considerably different outcomes:

Watchful Waiting or Active Surveillance

Surgery

Radiation Therapy

- External Beam Radiation Therapy (EBRT)

- 3-D CRT, IMRT, IGRT and Tomography

- Stereotactic Body Radiotherapy (SBRT)

- Proton Beam Therapy (PBT)

- Low Dose Brachytherapy (Seeds)

- High Dose Brachytherapy plus X-Ray Radiation

- PSMA Lutetium-177 Ligand Therapy

Hyperthermia

Cryotherapy

High Intensity Focussed Ultrasound (HIFU)

Focal Laser Ablation (FLA)

Hormone Therapy

Chemotherapy and Immunotherapy

Complementary and Alternative Therapies.

We look at these in appropriate detail in Chapters 6 to 16. At the end of each of these chapters, a summary of the treatment is outlined in easily-understood language and a partial set of pros and cons for and against the treatment are listed.

Chapter 6.

Active Surveillance (or Watchful Waiting)

Active Surveillance and Watchful Waiting are often regarded as being the same. Sometimes the term ‘Observation or Observational Management’ is also used.

Watchful Waiting - the urologist may advise that treatment is not required. This is more likely for men over 70 with a slow-growing cancer. However, it is important for PSA levels to be regularly monitored and a DRE be done to check for any abnormalities that might develop. Older patients with slow-growing low-grade cancer are more likely to die of a cause other than prostate cancer. If the PSA levels starts to elevate or irregularities are found after a DRE, it is likely that one of a number of interventions will be prescribed.

Active Surveillance - no standardised definition for Active Surveillance appears to exist. One study of 16 cohorts used different monitoring protocols, all with different combinations for DRE, PSA, re-biopsy and/or imaging findings. These different protocols also appeared to present differences in curative and palliative treatment objectives.[1] Active surveillance is an appropriate option for men with low volume, low risk prostate cancer. This approach maintains quality of life and provides excellent cancer survival rates. Currently, candidates for active surveillance (including watchful waiting) constitute approximately half of all men with newly-diagnosed prostate cancer.

The US National Comprehensive Cancer Network (NCCN) has recently updated their Prostate Cancer Guidelines™. The NCCN Guidelines for Patients® 2018 attempts to standardise Active Surveillance protocols for low grade and intermediate risk prostate cancer sufferers. It is a most comprehensive 100-page essay on prostate cancer which is well worth viewing. Access it via Appendix 3.

"There are several variables that must be considered in order to tailor prostate cancer therapy to an individual patient and the NCCN Guidelines provide a solid framework on which to base these treatment discussions and subsequent decisions," said Dr James L. Mohler, who is the chairman of the NCCN Guidelines Panel for Prostate Cancer. "The current NCCN Guidelines recommend that at age 40, high-risk men begin annual PSA and DRE. All other men at age 40 should be offered a baseline PSA and DRE and if their PSA is 1.0 ng/ml or greater, they should receive annual follow-ups. If their PSA is less than 1.0, the NCCN Guidelines recommend that these men be early detected again at age 45," said Dr Mohler.[2]

The NCCN Guidelines have established a new 'very low risk' category that incorporates the strictest Epstein criteria from all definitions for clinically insignificant prostate cancer. In addition, active surveillance and only active surveillance is now the recommendation for many men diagnosed with prostate cancer. Men with low risk prostate cancer who have a life expectancy of less than 10 years and men with very low risk prostate cancer with a life expectancy of less than 20 years should be offered and recommended active surveillance.

Findings from a Canadian study of 452 men by Klotz, et al., suggested that the 10-year actuarial survival rate of low-grade prostate cancer on an active surveillance protocol was 97.2%.[3] What constitutes an active surveillance protocol? The Epstein criteria of clinically insignificant prostate cancer (CIPC) are the most widely used by urology professionals. It suggested parameters are: clinical stage T2 or less, Gleason Score of 6 or lower, PSA density 0.15 ng/ml or lower, and less than 33% positive cores on biopsy.[4],[5] It should be noted that C. Elders, et al., in a paper in the European Urologist in December 2009, found that the Epstein criteria may understate the true nature of prostate cancer in European men by as much as 25%. Thus, it cautions the use of the Epstein criteria as the sole basis for a treatment regime.[6]

Another paper on the web site of the Prostate Cancer Research Institute in the USA by Professor Laurence Klotz, Professor of Surgery, University of Toronto, is a most informative examination of matters pertaining to low risk (< Gleason 7) patients. This paper also thoroughly covers the issue of the rapid PSA doubling time (PSADT) which is a very important parameter in judging the degree of aggressiveness of the cancer. Access this paper via Appendix 3.

A search of published scientific papers suggests the following parameters for a candidate for active surveillance:

Generally, 55-year-old or younger with a PSA level of <10 ng/ml; with a Gleason Score of 6 or less; and TNM value of T1c or T2a (with one tumour of less than 50% of one lobe); 25% or less of cores positive for cancer; with a PSA density of less than 0.15. For men older than 55, the PSA level might be 10 – 12 ng/ml or slightly higher for men in their seventies.

The April 2014 Prostate Cancer Guidelines of the European Urology Association suggest the following parameters for active surveillance candidates:

Over 10 years of life-expectancy, cT1-2, PSA ≤ 10 ng/ml, biopsy Gleason score ≤ 6 (at least 10 cores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).[7]

It is essential that you get specific advice from your medical team as regards your possible suitability to go on an active surveillance program. Urologists universally agree that it is very important for men adhering to an active surveillance regimen, to make a strict commitment to regular PSA and DRE testing AND an annual or two-yearly biopsy. The PSA and DRE should be done quarterly in the first year, followed by six monthly tests thereafter assuming that results stay within limits acceptable to your medical practitioner.

Should there be an adverse change in your results, the medical practitioner is likely to call for active intervention. It is probable that around 30% of active surveillance patients will require active intervention within a 5-year period of initial cancer diagnosis.

To put things into perspective, research by Dr Sung Kyu Hong, et al., from the Seoul National University Bundang Hospital[8] has shown that the clinical and biopsy-related parameters currently available, have limited value in the prediction of pathologically insignificant or unfavourable prostate cancer in patents with a single positive core and low PSA level. Further efforts are and should be made to identify more accurate predictors of actual pathological characteristics and/or prognoses of prostate cancers to improve the selection of candidates for active surveillance or alternatively active intervention.

The ‘Cancer Anxiety Factor’ is a powerful psychological circumstance that afflicts all men when told that they have prostate cancer. Many feel that they have to take positive action to rid their body of this treacherous and often fatal disease. Unfortunately, many urologists with the best of intent, advise their patients to undertake active intervention, which plays right into the patient’s frame of mind of wishing to be free of the threat. Institutions and most urologists in private practice recognise the patient’s vulnerability at that time and provide psychosocial support that might assist the patient to make a decision to join an active surveillance program. Most prostate cancers diagnosed today are Stage T1c, suggesting the biopsy was undertaken purely on the basis of an elevated

PSA and no DRE abnormality. While many threatening cancers are detected at this stage (T1c), over-treatment of T1c prostate cancers is now a concern to medical administrators.

Summary – Active Surveillance and Watchful Waiting

There is often confusion in the exact meaning of these two terms. A consensus for watchful waiting probably suggests less testing and intervention than in active surveillance and more reliance on changes in a man's symptoms to trigger a medical response. Active surveillance calls for a specific and regular testing regime including a DRE, PSA testing and in some instances, a biopsy and even imaging.

More than half of all men diagnosed with low risk disease conform well to an active surveillance regime.

Various international guidelines suggest slightly different parameters for active surveillance candidates.

Prostate cancer is generally a slow progression disease. Don't let the 'Cancer Anxiety Factor' push you into a more aggressive treatment option than is dictated by the prognosis data.

Chapter 7.

Surgery

The surgical removal of all (Radical) or part (Simple) of the prostate gland is called a prostatectomy. Multiple surgical approaches exist for both of these operations. A simple prostatectomy is used in the treatment of Benign Prostatic Hypertrophy, while a Radical prostatectomy is generally used in the treatment of early or intermediate stage prostate cancer. The simple prostatectomy is outside the scope of this book.

Radical prostatectomy is sometimes referred to as open prostatectomy, as the procedure sees an ‘opening’ or incision being made in the patient’s abdomen or perineal area, depending on which procedure is being undertaken: radical retropubic prostatectomy (RRP) – operate via the abdomen or radical perineal prostatectomy (RPP) – operate via the perineal area between the scrotum and the anus.

Radical retropubic prostatectomy (RRP) is a surgical procedure in which the prostate gland is removed through a 100 mm incision in the abdomen. It is most often used to treat men who have early-stage prostate cancer. RRP is usually performed under general anaesthetic and may require blood transfusions in less than 20% of cases. Common complications of a RRP are urinary incontinence and impotence. These outcomes are dependent on the experience and skill of the surgeon, the technique used and the physical anatomy of the patient. The most common surgical approach is to make a small incision in the skin between the umbilicus and the top of the pubic bone. The important structures in the pelvic region such as the prostate, bladder, urethra, blood vessels, and nerves are identified. Nerve-sparing surgery attempts to protect the neurovascular bundles which control

erections. These nerves run next to the prostate and may be damaged or destroyed during surgery, leading to impotence. An important part of the operation is to protect the cavernous nerves to minimize impotency and to maintain urinary control. During surgery, the surgeon may apply a small electrical stimulation to these nerves and measure the erectile function with a penile plethysmograph. This test aids the surgeon in identifying the nerves, which are difficult to see.

The prostate is separated from the urethra below and the bladder above, and the bladder and urethra are reconnected. The blood vessels leading to and from the prostate are then divided and tied off. The prostate, seminal vesicles, ends of the vas deferens, and, depending on oncological considerations, nerve bundles and/or pelvic lymph nodes are removed. A catheter is maintained in the urethra for up to about a week after the operation.

Radical perineal prostatectomy (RPP) has become a less popular surgical procedure due to limited access to lymph nodes and the difficulty in avoiding nerves.

Laparoscopic Radical Prostatectomy (LRP) is a modern form of radical prostatectomy which has substantially taken over from the earlier open form of surgery. A laparoscopic radical prostatectomy does not require a large incision, makes no use of retractors and does not require the abdominal wall to be parted and stretched for the duration of the operation. It is a form of 'keyhole' surgery. A laparoscope is introduced into the sub-umbilical site (the area between the umbilical and pubic areas) and is used to guide the operation. The surgeon and assistant each use the other four sites (usually with up to 5mm long incisions) for the introduction of instruments. Laparoscopic radical prostatectomy and open radical prostatectomy differ only in how they access the deep pelvic area and generate operative views. In contrast to open radical prostatectomy, LPR, in the hands of a capable and experienced urological surgeon, sees very little blood loss, little post-operative pain and less chance of infection. Some LRP

procedures include the use of robots. They are referred to as Robotic-Assisted Laparoscopic Prostatectomy (RALP) or Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP). These are both the same procedure.

The most well-known such robot laparoscopic system is the da Vinci® Prostatectomy System (Intuitive Surgical Inc., California, USA). The manufacturer claims on their web site that 4 out of 5 prostatectomy operations in the USA are performed on their system. Over 1.5 million patients have been treated on their systems for a range of conditions. The da Vinci® System features a magnified 3D high-definition vision system and special wristed instruments which are able to bend and rotate far more than the human wrist. It also contains tremor filtering technology. da Vinci® enables the surgeon to operate with enhanced vision, precision, dexterity and control. A da Vinci® prostatectomy offers the following potential benefits compared to traditional laparoscopy:

More patients return to pre-surgery erectile function at 12-month checkup

Faster return of urinary continence

Lower risk of complications

Less blood loss and need for a transfusion

Less chance of nerve injury

Less chance of injuring the rectum

Shorter operation

Less risk of deep vein thrombosis (life-threatening condition where a blood clot forms deep in the body)

Shorter hospital stays

Less chance of hospital readmission

Less chance of needing follow-up surgery.

More details and the references listed above are accessible via Appendix 3.

An important general advantage that RALP systems offer over the open surgery technique is an improved visual access of the operative field, particularly behind the pubic bone. This is achieved by use of a laparoscope that provides bright and even illumination of the magnified field of view and an image on a monitor that is able to be viewed by the surgeon, the assistant and scrub nurses in real time. This facilitates better team work by the surgeon and his assistant and a more precise dissection, which, in turn, provides better control of potential sources of bleeding.

As is the case in open prostatectomy, robotic radical prostatectomy entails the removal of the whole prostate and seminal vesicles. They are withdrawn generally through one of the 5 mm long incisions. Occasionally, it is necessary to extend the incision to extract a larger prostate. On occasion, particularly with patients with immediate risk (advanced localised) cancer, the surgeon might remove some lymph nodes near the prostate to see if the cancer has spread beyond the prostate. If the pathologist reports cancer in the lymph nodes, the surgeon will recommend further treatment, because the cancer is no longer localised. Sampling of the lymph nodes adds further time to the length of the operation, particularly so for the RALP technique.

During the RALP procedure the patient is placed in a steep ‘head down’ position, which on rare occasions leads to anaesthetic complications. After the operation, the surgeon will send the tissue they removed to the laboratory. The aim of the surgery is to remove all the cancer with a safety margin of cancer free tissue around it. This safety margin is called a clear margin. Should the pathologist find cancerous cells at the extremity of the removed tissue or in any removed lymph node tissue, it is likely that a course of radiation will be recommended. A key consideration in deciding to undergo a RALP operation is to determine the experience of the surgeon undertaking the operation.

Surgeons, who are proficient with both keyhole systems, appear to take a similar average length of time to perform the surgery of about 150 to 180 minutes. Average blood loss in a recent study was 533ml. In a 2001 study, it was reported as being 354 +/- 250 ml. Other studies report even lower blood losses with only very few patients requiring blood transfusions. François Rozet, Jamison Jaffe, et al. reported after a comparison of conventional laparoscopic to robot assisted laparoscopic prostatectomies within their institution that the conventional technique provided comparable results to those obtained by the RALP procedure.

The Background of Radical Prostatectomy

Radical prostatectomy is generally regarded as the most reliable treatment to cure prostate cancer. It is considered to be the ‘golden standard’ treatment.[2] From its introduction just after the 2nd World War, radical prostatectomy was associated with a high percentage of patients experiencing erectile dysfunction and/or incontinence after surgery. The precise pathway of the nerves mediating erectile function was reported by Dr Lepor in the early 80’s. Based on these discoveries, Drs Walsh and Lepor described a nerve sparing radical prostatectomy which greatly improved the likelihood of preserving erectile function following surgery.[3]

Dr Lepor has been a prolific publisher of scientific studies on erectile dysfunction after a radical prostatectomy. Prior to 2000, he reported that 40% of all men undergoing the surgical procedure will develop erectile dysfunction. This was despite the fact that he co-developed the surgical procedure and has performed more than 4500 radical prostatectomies. He reported the likelihood that erectile function will be preserved is dependent on many criteria including age, erectile function before surgery, if both nerves can be preserved and if cardiovascular co-morbidities are present. More recently, he co-authored a paper that reported on a total of 1,110 men undergoing open radical retropubic prostatectomy by a single surgeon, found 34% were not potent, post-operatively.[4]

A 2013 paper, ‘Advances in Robotic Assisted Laparoscopic Prostatectomy over Time’, by Emma F. P. Jacobs, et al., reviewed the advances made in the perioperative management and surgical technique of RALP.[5] This is paper is well worth reading.

Over the years, there have been numerous subtle and substantive changes to the surgical techniques using robotic assistance or conventionally. Despite these changes in surgical technique, many men still experience erectile dysfunction and/or incontinence. The increased use of the RALP technique has seen lesser blood losses, a shorter hospital stay and has resulted in very low 6% positive margins in cases of organ-confined disease. As Dr Thomas E. Ahlering, MD, of the University of California, Irvine, states on his web site:

"Prior to the Da Vinci® robot, it was very difficult to make such a clean and refined excision of the apical region of the prostate." [6]

An interesting table exists on the da Vinci® Surgery web site that compares patient outcomes for open, laparoscopic and da Vinci® RALP surgery. Access the web site via Appendix 3.

Outcomes and Side Effects

The 'Holy Grail' in the treatment of prostate cancer is an approach that reliably eradicates prostate cancer while preserving erectile function and urinary continence. This is an outcome that is impossible to guarantee, within the confines of present medical technology. In the main, the surgery option is only offered to men with local or advanced local disease. This increases the results for these men being cancer free years after the surgery. An Australian report[7] indicated cancer-free outcomes as follows:

After 5 years: - 75 to 85% cancer free

After 10 years: - 70 to 80% cancer free

After 15 years: - 60% cancer free

(These figures have been rounded to the nearest 5%)

Survival rates for men who have had cancer after having had surgery are also impressive:

After 5 years: - 96 to 98% survival

After 10 years: - 90 to 96% survival

After 15 years: - 81 to 82% survival

In a recently published research paper, JJ Park, et al.,[8] found that a pre-prostatectomy 3 Tesla field strength multiparametric MRI using a phased-array coil, including T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), was a significant independent indicator of biochemical recurrence of the cancer when the results of all three techniques were combined. After a median follow-up of 26 months, biochemical recurrence developed in 22% of patients out of the 282 men in the study. This finding stresses the importance of having regular post treatment PSA testing.

Before you make a final commitment to have surgery, ask yourself the following questions:

Have you sought a second opinion?

Have you contacted a prostate cancer support group for input?

Do you fully understand the side effect risks that can significantly alter your quality of life?

Have you fully discussed your choice with your wife or partner?

Are you ‘blindly’ following your urologist recommendation to have surgery?

Do you ‘just want the cancer out of my body’?

If you answered no to the first four questions and yes to the last two questions, it might be appropriate to step back and take stock of what you are facing.

Questions you should ask your surgeon after you have made a commitment to have surgery:

What exact type of surgery do you propose? (Open RRP; RPP, RLP or RALP?)

How many of these operations have you done and how many do you do a year?

What are your results?

Do you keep a data base of these results?

Will you try to do the nerve sparing surgery?

Will you remove any lymph nodes?

How long does the operation take?

Should I donate my own blood prior to surgery?

When should I stop aspirin (or warfarin) prior to surgery?

What about other supplements?

How long will I be in the hospital?

How do I take care of my catheter?

When will I have my first post-operation appointment?

What if I see blood in my urine?

When do I start exercising after surgery?

What other activities can I do and when? Golf? Jogging? Bike Riding?

When can I drive? When can I return to work?

How long will I need to wear a urinary pad?

How soon will I recover an erection?

Should I use Viagra, Levitra or Cialis after surgery?

When can I have intercourse after removal of my catheter?

How long until my urinary control returns?

What fills the space of the removed prostate? Is the length of the erected penis different?

What type of ejaculation can I expect?

What is the chance of needing further treatment for cancer after surgery?

Summary – Surgery

Surgery is usually only offered to patients with prostate cancer that is confined ‘to the box’.

Surgeons do either open or laparoscopic (‘keyhole’) prostatectomies with access to the prostate via the abdomen. A few surgeons have reason to access the prostate region via the perineum (between the testes and the anus).

The use of robot-assisted prostatectomies using the da Vinci® Prostatectomy is becoming more and more common.

The experience of the surgeon undertaking the procedure is a critical factor in getting a good outcome. Figures well into the hundreds of successfully procedures, in some reviews, are considered essential.

Some Factors in favour of a Prostatectomy

After active surveillance, it is concerned the most common treatment for prostate cancer that is still ‘confined to the box’.

Keyhole surgery sees a rapid recovery and early return to work.

Pathology of the removed prostate can confirm an adequate margin, that is, no cancer cells were present on the extremity of the prostate.

It is possible to remove any cancerous tissue in nearby lymph glands or pelvic area during the procedure.

Some Factors against having a Prostatectomy

One is very dependent on the experience and skill of the surgeon.

A high percentage of patients have incontinence and impotency challenges.

Studies have shown that a biochemical recurrence of the cancer may occur in up to 22% of patients.

A possible need to harvest your blood prior to surgery.

Pelvic or Kegel Floor Exercises

To quote from the **Continence Foundation of Australia** web site:

"What are pelvic floor muscles?"

The floor of the pelvis is made up of layers of muscle and other tissues. These layers stretch like a hammock from the tailbone at the back, to the pubic bone in front. A man's pelvic floor muscles support his bladder and bowel. The urine tube and the back passage all pass through the pelvic floor muscles. Your pelvic floor muscles help you to control your bladder and bowel. They also help sexual function. It is vital to keep your pelvic floor muscles strong. See Appendix 3 for more detailed information from the above web site.

Pelvic floor exercises are sometimes referred to as ***Kegel*** exercises. The WebMD web site tells you more and is assessed via Appendix 3.

See page 254 for more details on how to handle incontinence issues that are likely to arise after a prostatectomy or other prostate cancer treatments.

Chapter 8.

Radiation Therapy

8.1. External Beam Radiation Therapy (EBRT)

Firstly, lets look at the main purpose of radiotherapy: simplistically to kill the cancer. How does it do this? It is given to produce DNA strand-breaks in cancerous cells, causing severe DNA damage to these cells and cell death. Radiotherapy has the potential to kill 100% of any targeted cells, but the dose required to do so would cause unacceptable side effects to healthy tissue. Therefore, radiotherapy can only be given up to a ‘safe’ level of radiation exposure.

Radiotherapy in its many forms (EBRT; IMRT; IGRT; conformal 3D-CRT; PBT; SBRT and the two formats of brachytherapy), together with radical prostatectomy remains the overwhelming treatment prescribed for the treatment of localized (early stage) and localized (intermediate risk) advanced prostate cancer. Radiotherapy is sometimes used as an adjunct therapy to other treatments, e.g. a short course of radiotherapy might follow a prostatectomy or a high dose brachytherapy procedure. Patients that present themselves with a PSA of greater than 10 and/or a Gleason score of 7 to 10, often undergo a course of hormone therapy plus EBRT, which has been shown to improve survival rates.

EBRT has been a main stream therapy for treating cancers for many decades. Its increase in use coincided with the introduction of improved linear accelerators (LINACS) in the 60’s. LINACS are devices that generate the x-rays used to treat cancers. EBRT treatment protocols call for the patient’s prostate to be exposed to short pulses of tightly focused beams of x-rays for a few minutes each day for five days a week for about 7 weeks. It is a painless procedure with no short-term noticeable side effects.

EBRT (and its later derivatives, IMRT etc.) deliver treatment outcomes for patients with low or intermediate risk tumours, with results that are closely comparable to that of surgery or brachytherapy. EBRT has also been shown to provide long term quality of life outcomes that are again broadly similar to surgery and brachytherapy.[1],[2] Patients that present with a PSA of greater than 10 and/or a Gleason score of 7 to 10, often undergo a course of hormone treatment plus EBRT, which has been shown to improve survival rates.[3]

Before the course of treatment begins, it is usual for a series of imaging procedures, such as MRI's, CT scans and normal x-rays of the pelvis/prostate area to be done, to locate the exact position, shape and size of the prostate. The radiation oncologist will calculate the exact dose to be delivered and develop a treatment plan specific to that patient. The radiation team may make a series of ink marks on the skin to assist them in directing the radiation to the prostate.

Combining radiation therapy with PARP inhibitors is a promising new development. The inhibitors lead to the formation of double-strand breaks from the single-strand breaks generated by the radiotherapy in tumour tissue with BRCA1/BRCA2 mutations. This combination has led to either more powerful therapy with the same radiation dose or similarly powerful therapy with a lower radiation dose. If you carry these mutations, discuss this new development with your medical team.

The advantages of EBRT versus surgery are:

It is less intrusive and stressful than surgery.

It avoids any risk of infection.

It is suitable for all ages and health conditions.

There is no need to harvest some of your own blood prior to undertaking surgery.

It might offer cost advantages dependent on the patient’s jurisdiction.

Its disadvantage versus surgery is the need to front up each working day for about an hour for at least 7 weeks (and sometime up to 9 weeks). The patient has only a few minutes exposure to x-rays, but the set-up procedures can take up to thirty minutes. For patients that are some distance from the treatment centre, the cost of travel and travel time are often not inconsequential.

EBRT generally leads to some radiation damage to the bladder and the bowel. Many EBRT patients experience mild to moderate bowel inflammation that manifests itself in the form of loose and more frequent bowel motions, and possible rectal bleeding. This might only occur six months to many years after radiation treatment concludes and may be an ongoing malady. About 3% of men develop severe and ongoing bowel problems. Rates of occurrence of incontinence and impotence are much less to those experienced by surgery patients. With EBRT, up to about half of men develop erection problems, some of which respond to remedial treatments, such as use of Viagra, etc.[4]

The skill of the radiation oncologist and the equipment used can make a marked difference in the outcomes achieved. Thus, it is important to understand your radiation oncologist’s success record using the same treatment parameters. With the newer variants of EBRT, outcomes are generally superior to those achieved with the older technology. This is mainly due to the ability to focus the radiation more accurately and at higher doses on the prostate and by reducing the radiation exposure to healthy adjacent tissue.

Jason A. Efstathiou, MD, DPhil, in a recent article[36] reflecting on the changing landscape of EBRT, suggested that prostate cancer management has shifted considerably. This has seen a rise in radical prostatectomies and in post-operative radiation therapy, as well as a proliferation of other radiation treatment options. The catalyst for these changes has been mainly due to the current recommendations for PSA screening having resulted in less screenings being performed and a higher incidence of men being diagnosed with high risk or metastatic prostate cancer.

He pointed out that in terms of radiation therapy, the NCCN currently supports EBRT with ADT; EBRT with ADT and brachytherapy; as well as EBRT with or without ADT, as adjuvant therapy following surgery in the setting of high or very-high-risk prostate cancer. Other considerations that he listed for the modern era were:

ADT should always be accompanied by radiation therapy. Large trials have shown clear benefit to cancer-specific survival and reductions in disease-related deaths.

Conversely, radiation therapy should always be accompanied by ADT, unless local control with radiation is possible.

Recommendations support dose escalation to assist in cancer control, but evidence shows no benefit to overall survival rates with this method. Also, toxicity is a concern that must be addressed.

Radiation and prostatectomy are both equally effective treatments for high-risk patients.

There is no proven difference in outcomes between whole-pelvis irradiation and prostate-only irradiation.

Radiologists continue to look for faster and better patient outcomes. To this end a Scandinavian Phase 3 trial into ultra-hypo fractionated versus conventionally fractionated radiotherapy for prostate cancer reported the 5-year outcomes of the trial in The Lancet Journal – June 19. Men in the ultra-hypofractionation group had a total dosage of 42·7 Gy in seven fractions, 3 days per week for 2·5 weeks versus men receiving conventional fractionated radiotherapy of 78·0 Gy in 39 fractions, 5 days per week for 8 weeks. The trial concluded no differences regarding failure-free survival and only slightly more pronounced side effects in the ‘ultra’ group in the first year. After 5 years no discernible differences in side effects existed. The importance of this is time, cost and inconvenience saved by using ultra-hypofractionation (high dosage) radiation.

What happens in the event that the cancer growth returns in the future after initial radiation therapy?

After your initial prostate cancer treatment, the medical staff will require you to have at least 6-monthly PSA tests to monitor the reduction in your PSA level over a 12 month period to a level of somewhere between 0 and 2 ng/ml. Approximately 30% of men treated for localized prostate cancer experience a biochemical relapse after their initial treatment.[5] This suggests a need to maintain vigilance for years after initial successful treatment by regular PSA testing. Two studies after radical prostatectomies found that the BCR incidences were 32% and 15% respectively.[6],[7]

If a problem exhibits itself in the form of a much higher PSA result, it is likely to be between 2 and 10 years after the original radiation treatment. (Shorter ‘recurrence’ periods of less than 2 years are probably ‘progression’ of the disease and not a recurrence). Several ‘salvage treatments’ are available which might include radical prostatectomy, cryotherapy, high-frequency ultrasound, chemotherapy or hormone treatment. It is not possible to have further radiation therapy, due to the urethra not being able to handle the same. It is reported that a ‘salvage’ prostatectomy is an extremely challenging procedure, with some specialists now starting to favour focused techniques like cryotherapy or HIFU (in countries were the latter technique is approved).[8]

After radiation therapy, PSA levels reach their nadir (lowest point) up to two years after treatment. A biochemical recurrence after radiation therapy is typically defined as three PSA increases above the nadir (lowest) PSA level measured at least two weeks apart by the same lab. A further definition, the ‘Phoenix consensus’, calls for the nadir value plus 2 to be used for BCR. Radiation therapy is also used to treat patients with metastatic prostate cancer (cancer that has spread beyond the prostate). This relieves symptoms of bone pain, obstructions or bleeding.

Note that the definition for biochemical recurrence is different in the case of a total prostatectomy as the PSA level drops to what might be regarded as zero after the operation. A biochemical recurrence after a radical prostatectomy is regarded as being present when a PSA reading of > 0.2 ng/ml increases in each of two further tests at least two weeks apart using the same lab.[9]

We have seen that rectal damage from radiation is a real challenge for prostate cancer patients. It affects all men undergoing radiation treatment (of all types and formats) to a greater or lesser degree. There is now a product available, which substantially eliminates the possibility of radiation damage to the bowel. It was approved for use by the FDA in the USA in 2015, with many other countries now following their lead. It’s called the SpaceOAR® System – Spacing Organs At Risk. SpaceOAR® hydrogel is injected as a liquid between the prostate and rectum under ultrasound guidance. Once injected, the liquid solidifies within seconds into a hydrogel that pushes the rectum away from the prostate. The result is reduced rectal radiation during radiation therapy. The hydrogel maintains space during radiation therapy for up to three months and then liquefies, allowing it to be absorbed into and cleared from the body (within six months). Access their web site via Appendix 3.

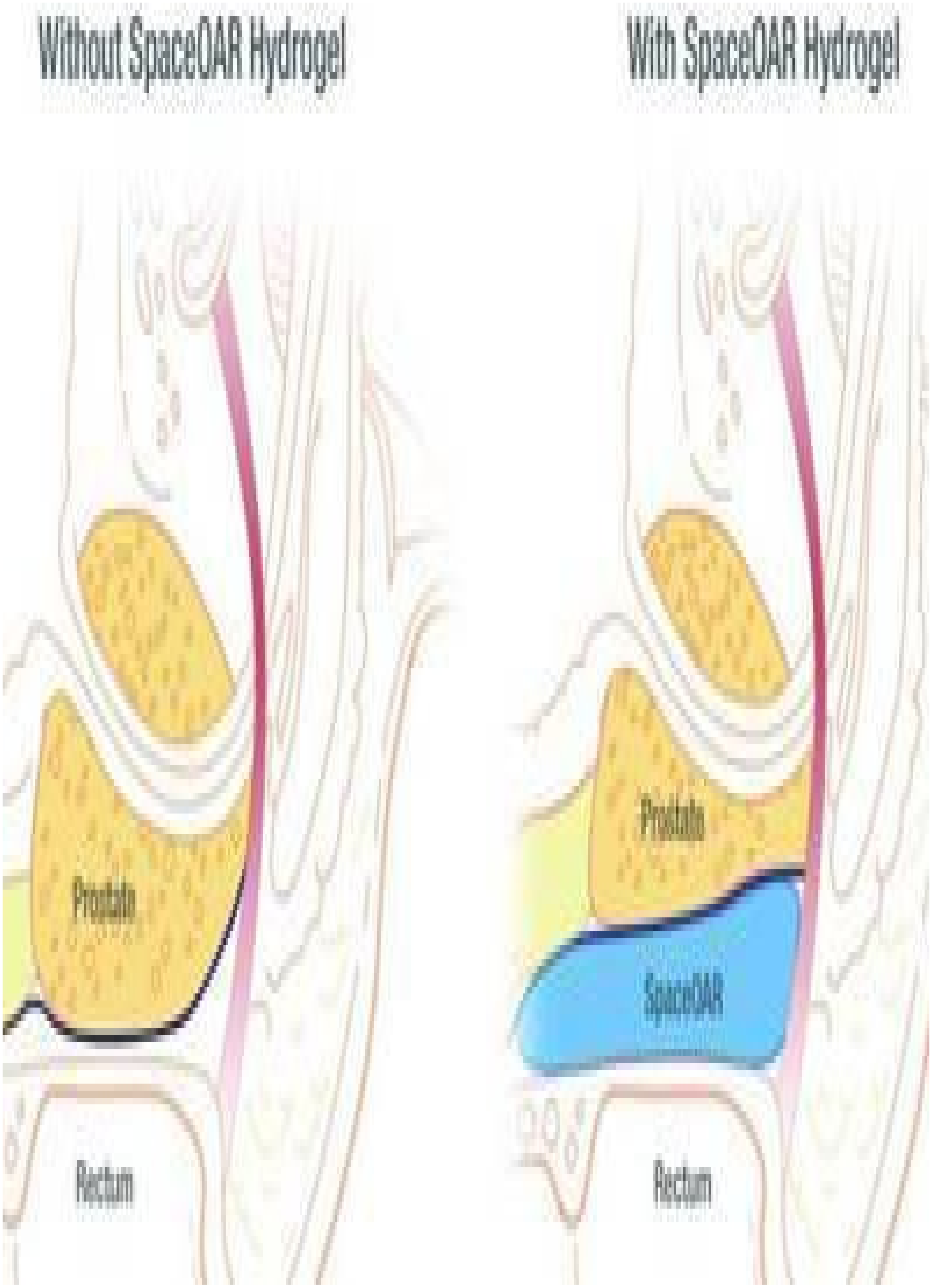
All forms of radiation therapy present the patient with some radiation exposure of the bladder and the rectum. Of course, some treatments offer less exposure than others with resultant lesser short, medium- or long-term damage to these organs. During a recent meeting with a leading urologist, he stressed the fact that radiation damage often takes up to five to ten years to manifest itself. He said that he regularly sees patients with blood in their urine (and other urinary complications) years after the radiation exposure.

Summary – External Beam Radiation

EBRT (and its later derivatives, IMRT etc.) deliver treatment outcomes for patients with low or intermediate risk tumours, with results that are closely comparable to that of surgery or brachytherapy.

Long term quality of life outcomes that are broadly similar to surgery and brachytherapy.

Later derivatives of EBRT generally give better outcomes than older systems.


Without SpaceOAR Hydrogel
With SpaceOAR Hydrogel
Prostate
Rectum
Prostate
SpaceOAR
Rectum

SpaceOAR Hydrogel Application

- Biocompatible
- Maintains space for ~ 3 months
- Absorbs in ~ 6 months

Image: Courtesy of Augmenix Inc

Factors in favour of EBRT

It is less invasive than surgery with no infection risk and is likely to cost less than surgery.

It suits all ages and health conditions.

Avoids the stress of an anaesthetic and surgery.

Some Factors against EBRT

Radiation damages the urethra, et al. In cases of a recurrence of the cancer, fewer salvage treatment options are available and greater difficulties occur in undertaking these options.

The patient needs to commit to daily treatment (weekdays only) for up to ten weeks.

Possibility of rectal burning (avoidable by using the SpaceOAR® hydrogel). Also, bladder difficulties such as blood in the urine, etc.

Higher risk of bladder cancer some 10 to 15 years after the radiation treatment.

8.2. 3-Dimensional Conformal Radiation Therapy, Intensity-Modulated Radiotherapy, Image-Guided Radiotherapy (3-D CRT, IMRT and IGRT) and Tomotherapy

The advance in the capabilities of imaging machines such as CT and MRI over the past two decades has led to the capability to accurately delineate tumours and adjacent normal structures in three dimensions. Improvements in radiation treatment planning software and the ability to shape the profile of the radiation beam to match that of the target by using multi-leaf collimators lead to the introduction of 3-dimensional conformal radiation therapy and subsequently, IMRT and IGRT and more. These developments reduced the radiation to the surrounding healthy tissue and allowed a higher radiation dose to be directed at the tumour.[10]

Intensity-modulated radiation therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of 3-D CRT. The LINAC (an x-ray linear accelerator) delivers precise radiation doses to malignant tumours or specific areas within the tumour under advanced computer control. The single radiation dose is delivered using a series of tiny beam-shaping devices called collimators. The collimators can be stationary or can move during treatment which allows the intensity of the radiation beam to be changed during treatment. This variance in dose intensity is called dose modulation, which sees different parts of the tumour and the healthy surrounding tissue, receive different radiation doses. This dose modulation provides better tumour targeting, reduced side effects, and improved treatment outcomes than the earlier 3-D CRT systems.

The pattern of radiation delivery is determined by the radiation oncologist, in conjunction with a medical physicist. They develop a treatment plan, which uses advanced computing applications to perform optimization and treatment simulation routines. The treatment plan also determines the multiple angles to be used to deliver the total radiation dose. It is advantageous to have as much energy as possible impact the tumour, whilst sparing healthy tissue by having multiple body entry points.

In IMRT, an inverse treatment plan is generally used. The inverse treatment plan sees the radiation oncologist choose the radiation doses to be delivered to different parts of the tumour and its surrounding tissue. The computer program takes the inputted data and calculates the required number of beams, their angles, etc. In traditional treatment plans, the number and angles of the beams is determined by the radiation oncologist, with the computer determining the dose level to be delivered by each of the beams.

With any cancer treatment, what is important is the outcome and to perhaps a lesser extent, the side effects that are experienced. IMRT has been in widespread use for about 20 years, after its introduction in the late 1990's. Anecdotally, it is considered vastly superior to its predecessor devices such as the EBRT and 3D confocal therapy systems. Certainly, it ensures reduced radiation exposure to healthy tissue and increased dosage to the tumour site than with earlier radiation systems. In fact, the control of the radiation beam is so good that some facilities with IMRT systems are now selectively offering IMRT as salvage treatment to men who have previously had x-ray radiation therapy.[11]

To illustrate the improvements that IMRT has provided with regard to reducing radiation damage to organs at risk, the results of a large study conducted on more than 1400 prostate cancer sufferers done at the Fox Chase Cancer Centre, Philadelphia, showed that the genitourinary side effects of the two treatments at three years post treatment were statistically similar, whereas there were lesser gastrointestinal (rectal) side effects reported for IMRT. This was despite higher doses being used for the IMRT treatments.[12] In a further study at the Fox Chase Cancer Centre, it was reported that, although 3D-CRT therapy combined with hormone therapy, produced excellent outcomes in intermediate and high risk patients, the patients treated with confocal radiation therapy were twice as likely to suffer gastrointestinal side effects compared with the group who had been treated with IMRT when measured at a mean follow up of 86 months.[13]

Image-Guided Radiation Therapy (IGRT) is a form of IMRT, which sees repeated image scans of the tumour area done by CT, MRI or PET immediately before treatment or during the treatment. The results obtained from the imaging scans are feed into the IGRT computer system for it to detect changes in the size or position of the tumour. These results are compared with the images stored in the system from the simulation done in the development of the treatment plan. The computer makes appropriate adjustments to the treatment area, thus ensuring maximum precision is made in radiation delivery.

ViewRay, Inc. announced in May 19 that the Siteman Cancer Centre at Barnes-Jewish Hospital and Washington University School of Medicine in St. Louis had treated its 1,000th patient using the MRIdian MR-guided radiation therapy (MRgRT). Siteman Cancer Centre helped pioneer MR-guided radiation therapy, becoming the first centre to treat patients with MRIdian in January 2014. ViewRay announced in September 19, the imminent journal publication of results of the first prospective clinical trial of MRgRT in patients with localized prostate cancer. This robust study reported outcomes demonstrating zero CTCAE v4 Grade 3 or higher gastrointestinal and genitourinary toxicity and even lower incidence of Grade 2 toxicity than investigators expected. It is also one of the first prospective clinical trials to study SBRT in a mix of intermediate- and high-risk prostate cancer patients, a challenging patient population to treat. Radiation therapy is really becoming fully of age, with these and other recent technology advances.

Tomo therapy is similar to IGRT. The machine is a hybrid between a CT imaging scanner and an EBRT machine. The radiation part of the unit has the capability to rotate completely around the patient as is done by a normal CT machine. Tomo therapy machines can capture CT images of the patient’s tumour immediately before treatment sessions which assists in the precision of radiation delivery. It is thought that, like standard IMRT, tomo therapy may be better at sparing healthy tissue from high radiation doses, but no clinical trials appear to have been done to compare 3D-CRT with

tomo therapy in a prostate cancer setting. Tomo therapy was found to have advantages over IMRT and 3D-CRT based on the dosimetric comparison in a post-operative breast cancer study, especially in the high dose region of lung, target homogeneity and dose uniformity.[14]

Dosage

Around the world the standard dosage for radiation therapy appears to be 70.2 Gy. However, over a period of years, the dosage usually delivered in the USA has increased to 79.2 Gy, which is regarded elsewhere as dose-escalated RT. In September 2014, a trial by a group of 104 US centres, collectively known as the Radiation Therapy Oncology Group (RTOG) 0126, reported its findings. The trial compared high-dose RT (79.2 Gy) with standard-dose RT (70.2 Gy) in the treatment of more than 1500 men with intermediate-risk prostate cancer. It found that there was no significant difference in overall survival between men in the high-dose group and men in the standard-dose group (66.7% vs 65.6%). It did report higher instances in both gastrointestinal (GI) and genitourinary (GU) toxicity with the higher dose patients. However, it did report that dose escalation did improve local control and distant metastases-free and biochemical disease-free survivals, but with accompanying increased GI and GU toxicity.

Summary - 3-D CRT, IMRT and IGRT and Tomo therapy

All the above systems under the control of a good radiation oncologist should provide better outcomes than provided by an older EBRT system.

The use of advanced software routines, multi-leaf collimators, changes to the dose presented to different parts of the tumour, all work to minimise the radiation dose received by healthy tissue and increase the radiation dosage to the tumour site.

IGRT is able to track movements in organs whilst the patient is under treatment and adjusts the direction and intensity of the radiation dose to compensate for these movements, thus ensuring an optimal radiation session.

Increased dose delivery increases future metastases-free and biochemical disease-free survivals, but with accompanying increased GI and GU challenges.

It may be used to ‘top-up’ the radiation dose after brachytherapy.

Some Factors in favour of 3-D CRT, IMRT and IGRT, etc.

IMRT control has now improved to the extent that it can be used in select cases of cancer recurrence in patients previously treated with radiation.

It offers less damage to healthy tissue than earlier EBRT systems. GI and GU difficulties are being lessened which supports an improved lifestyle.

Some Factors against the use of 3-D CRT, IMRT and IGRT, etc.

The patient needs to commit to daily treatment (weekdays only) for up to ten weeks.

Possibility of rectal burning (avoidable by using the SpaceOAR® hydrogel).

Also, possible bladder difficulties such as blood in the urine, etc. as a result of radiation ‘scatter’.

A lower risk of bladder cancer when compared with older EBRT systems years after the radiation treatment.

8.3. Stereotactic Body Radiotherapy (SBRT)

Stereotactic radiation is a specialised form of external beam radiation therapy (EBRT). It uses focused radiation beams to target the tumour. The radiation dose is delivered with extreme accuracy by utilising detailed imaging, computerised 3-D treatment planning and precise treatment set up. It is a treatment for low and intermediate risk prostate cancer patients. There are two types of stereotactic radiation: Stereotactic radiosurgery (SRS): a single or multiple stereotactic radiation treatments of the brain or spine. SRS is outside the scope of this book. Stereotactic body radiation therapy (SBRT): one or several stereotactic radiation treatments to parts of the body, excluding the brain or spine.

A number of machines are available for SBRT treatment of the prostate. These include the Rapid Arc (marketed as a volumetric arc therapy system); the Accuray's CyberKnife® and Tomo Therapy®; Elektra's Axesse®and Synergy®S; Varian Trilogy®; Siemens Oncor® and the Novalis X-Knife® Tx radiation system. All these systems use x-rays (photons) to irradiate the tumour. Most of these systems also incorporate the capability to move the radiation dose being delivered to conform to movements of the tumour due to organ movement, e.g. rectal or bladder. The image guidance systems identify the exact position in the prostate of three implanted gold seed markers called fiducials. (These are implanted in a process similar to biopsy sampling). The fiducial positions are continually reported by the image guidance system to the intensity modulated beam system that is shaped to fit and surround the prostate gland, aiming at the prostate gland continuously as the gantry rotates through 360 degrees around the patient. One such specialised beam system is called RapidArc®.[15]

This system combined with the Novalis Tx, contains a treatment planning algorithm that simultaneously changes three parameters during treatment:

Rotation speed of the gantry.

Shape of the treatment aperture using the movement of multi-leaf collimator leaves.

Delivery dose rate.

The RapidArc® volumetric modulated arc therapy system differs from other systems like helical IMRT or intensity-modulated arc therapy (IMAT) as it delivers its dose to the whole volume of the tumour (and its safety margin) rather than slice by slice as in other systems. The accuracy of these new technologies allows the margin around the prostate to be reduced, thus significantly reducing the side effects to the rectum and bladder.

The American Society for Therapeutic Radiology and Oncology (ASTRO) Emerging Technology Committee's report on SBRT for prostate cancer is recommended reading for the technically-minded.[16] The key advantage of SBRT is it delivers the right amount of radiation to the cancer in a shorter amount of time (usually 5 treatment sessions of about 15 minutes each as an outpatient) and generally more accurately than other radiation treatments.[17] Dr Chris King of UCLA was an early pioneer in the use of SBRT and in 2010 published an update of his clinical SBRT trial, now with 2.7 years median follow-up, where he has shown that the late side effects are minimal, similar in nature to those described for standard external beam radiotherapy, and often less frequent than seen with the standard radiotherapy courses.[18]

With prostate cancer, the proximity of the bowel and bladder might limit the radiation dose applied. Radiation exposure to the rectum and bladder is considered equal or better than brachytherapy and cancer control outcomes are reported as equivalent to those of brachytherapy, conventional external beam radiation or surgery. The side effects experienced are generally somewhat greater than those experienced with conventional external beam radiotherapy. The cost of the procedure was found to be significantly lower than IMRT.[19] (This study covers the period 2008 to 2011, when SBRT was in its initial years of use. It is likely that outcomes have improved with better operator experience and training since 2011 – This improvement has been confirmed in recent Phase 2 studies).

The CyberKnife® Robotic Radiosurgery System delivers radiotherapy to the patient with greater precision and accuracy than standard radiotherapy systems. It consists of a small linear particle accelerator that produces the radiation beam and a robotic arm which allows the energy to be targeted and delivered to any part of the body from any direction. The mounting of the radiation source on the robot arm allows maximum freedom to rapidly move the source to deliver radiation doses to the patient from multiple directions sequentially. It also includes an image guidance system allowing the system to compensate for minor organ movement. The system incorporates x-ray imaging cameras which are mounted on supports around the patient allowing real time x-ray images to be obtained.

The CyberKnife® has been around for nearly 30 years with more recent models being vastly superior to the earlier models. Their latest M6 system was installed in Perth in West Australia in 2013 and offers prostate cancer treatment for Australian and a limited number of international patients.[20] Although its name may suggest surgery, the CyberKnife® does not involve cutting at all. It is purely a radiation delivery device, albeit a very sophisticated one. The system is also used for 3D-CRT and IMRT. The CyberKnife® has treated more than 150,000 cancer patients with more than 10,000 having been treated for prostate cancer.

SBRT has now been proven to be effective in treating low risk or favourable intermediate risk men with localised prostate cancer.[38] It is also used to irradiate ‘spots’ in metastatic prostate cancer. This often yields lower PSA values, less pain and slower progression of the disease.

What questions should I ask my Specialist about external beam radiation therapy (all variants)?

Will I be treated as an outpatient? (No hospital stay)

How many radiation sessions will I need?

What can I do to prepare myself for the radiation treatment?

What can I do to speed my recovery?

Should I get a second opinion? If not, why not?

Is the radiation painful and are their short-term side effects?

How can I avoid radiation damage to the rectum?

What are the health risks from radiation? Erectile dysfunction? Incontinence? Rectal damage?

What form of machine (EBRT; 3-D Conformal; IMRT; etc.) might be used for my radiation? Is it the best available to me? If not, why not?

If there is a future recurrence of the cancer, what ‘salvage’ treatments are available?

Is there a prostate cancer support group that you might recommend?

Am I likely to get as good an outcome as: surgery; brachytherapy (both types), other treatments?

What will the radiation sessions cost? What percentage will be covered by Medicare? What percentage will be covered by my private health insurance? What percentage will I have to bear out of my own pocket?

What if I have had previous prostate surgery, TURP or bladder neck incision?

Will I still be able to father children after the radiation session?

After the radiation treatment is complete, what is the follow up procedure? Short-term? Longer term?

Summary – SBRT

Radiation exposure to the rectum and bladder is considered equal or better than brachytherapy and cancer control outcomes are reported as equivalent to those of brachytherapy, conventional external beam radiation or surgery. The side effects experienced are generally somewhat greater than those experienced with conventional external beam radiotherapy.

A key attribute of the use of SBRT systems in treating prostate cancer is the escalation of dose which allows a full dosage to be delivered in 5 or less radiation sessions. The sophisticated control of the radiation beam that is usually delivered through 360o with the ability of the system to compensate for organ movement during radiation delivery, provides acceptable radiation exposure to the prostate.

8.4. Proton Beam Therapy

A Brief Look at Standard Radiation Therapy

Everyone has had an x-ray at some time or other. These days CT scans are done as a diagnostic aid on a regular basis. These all involve parts of the body being irradiated with x-rays in the form of photons. A normal chest x-ray provides the patient with about the same radiation dose as would be received in 10 days from background radiation. A CT scan would provide many times this level of radiation. Radiation therapy for treating cancer provides considerably higher radiation exposure to the patient than via a CT scan, with the energy in the radiation beam irradiating healthy as well as cancerous tissue before and after the tumour. This leads to undesirable side effects and in worst cases, triggers secondary cancers due to the exposure of the healthy cells to high doses of radiation.

All radiation therapy works by damaging the DNA of the cells that the radiation interacts with, and the goal is to deposit as much energy (or dose) as possible to the tumour site while minimizing the dose and associated damage to the surrounding healthy tissues. Many approaches have been taken to reduce the radiation damage to healthy tissue adjacent to the tumour. These include irradiating the tumour from different angles; modification of the beam to match the tumour shape; and modulating the intensity of the radiation delivered to different parts of the tumour. More recently, technical advances have allowed the tumour to be irradiated from all around the patient. Even with these advances in radiation delivery, the collateral damage to healthy tissue and the limitations on the maximum dose exposure to healthy tissue are still a concern.

What is Proton Therapy?

Proton therapy is an external-beam radiation therapy technique not dissimilar to conventional high energy x-rays. The difference is that protons are heavy charged particles that deposit their radiation dose in a very precise targeted manner. When protons enter the body, they have little lateral scatter in the body tissue with the beam hardly broadening. They leave a minimal amount of energy along their path as they pass through healthy tissue on their way to the target tumour. When they reach the target depth (the tumour), the protons deposit a large focused amount of energy on the target and then dissipate, leaving almost no energy beyond the targeted depth. The protons, which are relatively high mass charged particles, damage the DNA of cells, ultimately causing their death or interfering with their ability to proliferate. Cancerous cells are particularly vulnerable to attacks on DNA because of their high rate of division and their reduced abilities to repair DNA damage due to their poor blood supply, etc.

This ability of the protons to deposit almost all of their energy at a specific depth is referred to as the Bragg Peak Effect which was discovered by William Bragg in 1904. In modern proton therapy systems, the depth of the Bragg Peak is accurately controlled by changing the energy of the protons, thus allowing clinicians to precisely tailor the proton dose to the specific depth and shape of the tumour while minimizing the dose to surrounding healthy tissue. The advantages of proton therapy over conventional radiotherapy are significant in areas of the body with critical adjacent structures such as the eye, brain, base of the skull, spine, and prostate. These advantages also extend to paediatric cancer patients.

Protons of different energies with Bragg peaks at different depths are usually applied to treat the entire tumour.

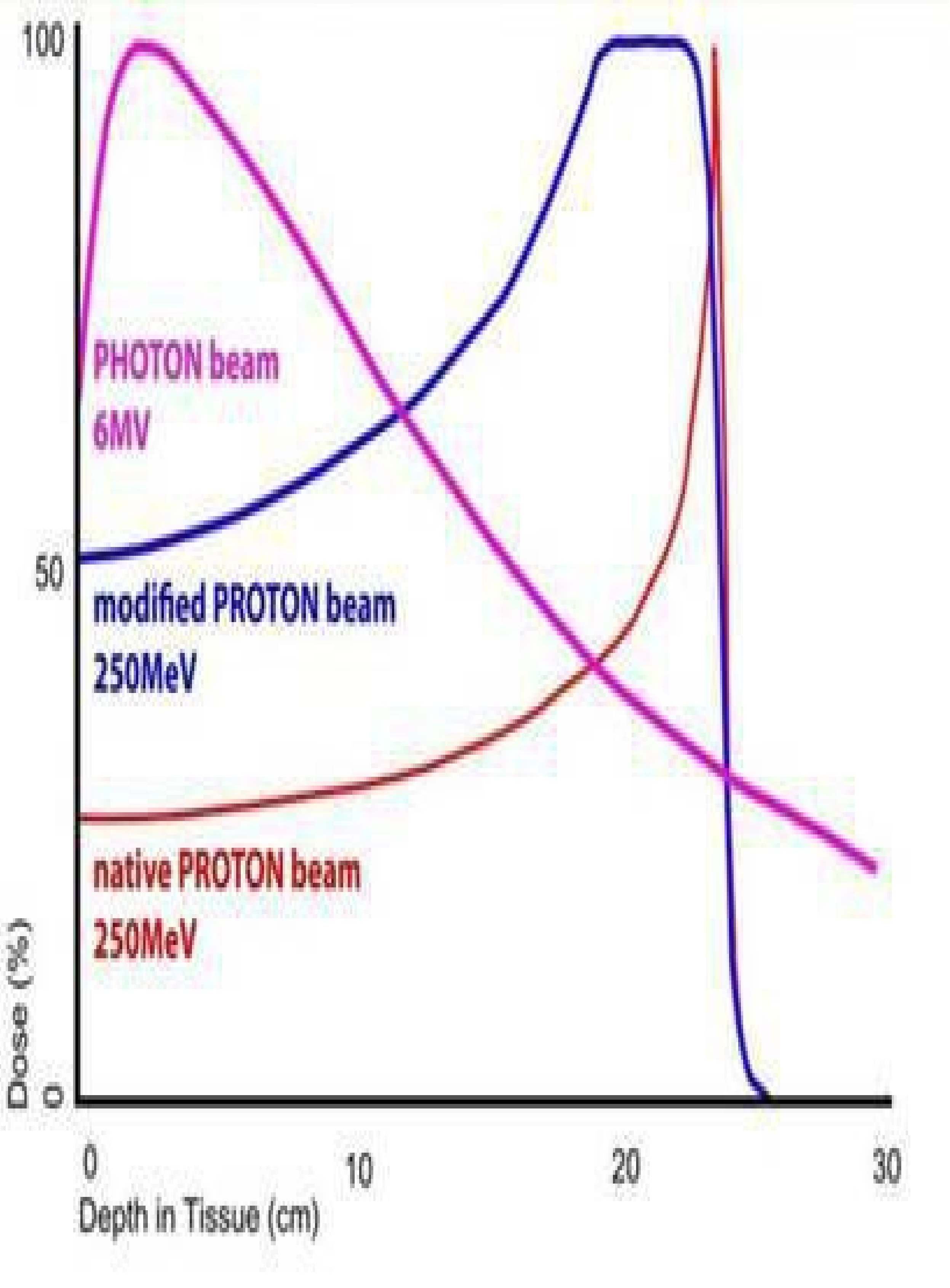

100
50
0
Dose (%)
PHOTON beam
6MV
modified PROTON beam
250MeV
native PROTON beam
250MeV
0
10
20
30
Depth in Tissue (cm)

Image: Courtesy of Wikipedia

In a typical treatment plan for proton therapy, the Spread-Out Bragg Peak (SOBP, dashed blue line - see the image below), is the therapeutic radiation distribution. The SOBP is the sum of several individual Bragg peaks (thin blue lines) at staggered depths. The depth-dose plot of an x-ray beam of photons (red line) is provided for comparison. The pink area represents the additional dose delivered by x-ray radiotherapy which can be the source of damage to normal tissues and of secondary cancers, particularly of the skin.

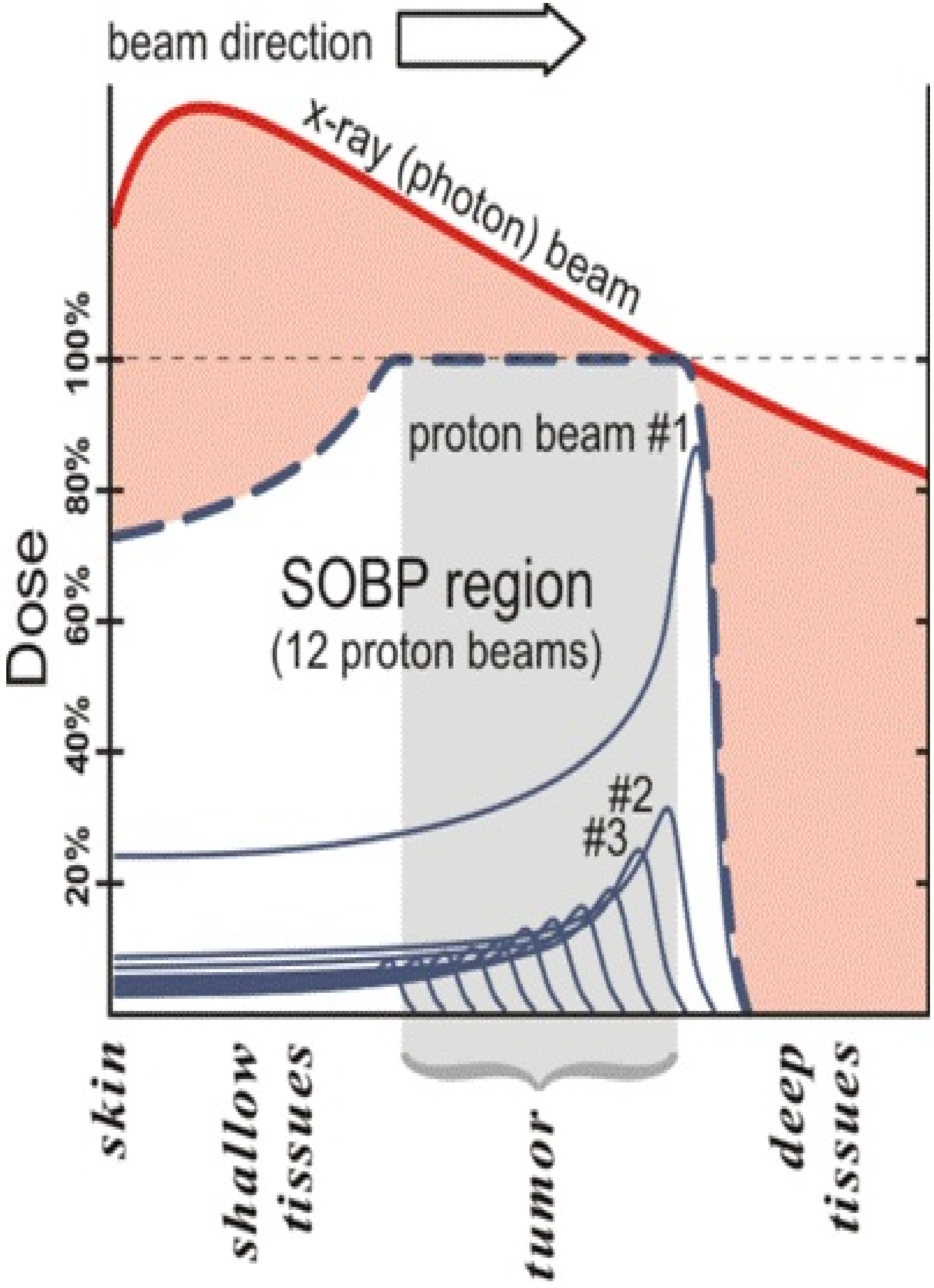

beam direction
x-ray (photon) beam
Dose
100%
80%
60%
40%
20%
proton beam #1
SOBP region
(12 proton beams)
#2
#3
skin
shallow tissues
tumor
deep tissues

Image: Courtesy of Wikipedia

So How Does it Work?

Protons are positively charged particles – the nucleus of the hydrogen atom. Free protons are produced by ionisation of hydrogen atoms into positively charged protons and negatively charged electrons stripped from a hydrogen gas supply. The protons are injected via a vacuum tube into a linear accelerator, and in a few microseconds, their energy reaches 7 million electron volts. Free protons enter the centre of the synchrotron or cyclotron, and are guided in a circular path by a powerful magnet and are accelerated to higher and higher energies. As they gain energy, they spiral outwards to the edge of the cyclotron magnet by which time their energy has increased to a total of 70 million to 250 million electron volts, which is sufficient to reach any part of the patient’s body. When they achieve speeds of about two-thirds of the speed of light (100,000 miles per second), a high voltage deflects them out of the system into a beam line, which via a vacuum line guided by other magnets, presents the proton beam to the treatment room. Prostate cancer patients are treated in a gantry treatment room with the gantry rotatable through 360 degrees, which allows the beam to be delivered at any angle. The whole system is controlled by a network of computers and extensive safety systems and protocols. The protons finally enter the nozzle system where the beam is shaped as it passes through a patient specific aperture, before it reaches a compensator that exactly reflects the shape and size of one half of the patient’s prostate. Passage through the compensator shapes the protons into a precise and unique 3-D profile with delivery of the most effective radiation dose in that profile to the prostate. The cell damage inflicted by the proton radiation is maximized within the tumour itself, by adjusting the energy of the protons during the treatment.

Most proton therapy systems include a patient position verification system that is interfaced to a treatment planning system (or an oncology information system). This facilitates the integration of the treatment plan with the reconstructed radiographs that enable patient positioning to within sub-millimetre accuracy.

A Short History of Proton Beam Therapy

Dr Robert Wilson first proposed the use of protons for cancer treatment in 1946 when he was working on the design of the Harvard Cyclotron Laboratory (HCL). In 1951, the first clinical treatments were performed at the Berkeley Radiation Laboratory in the USA using linear accelerators, which were designed for physics research and the space program. Ten years later collaboration began between HCL and the Massachusetts General Hospital (MGH) to pursue proton therapy. Over the next 40 years, this program progressed proton beam therapy while treating almost 10,000 patients before the Cyclotron was replaced by a new system at MGH in 2002. In 1990, the first clinical system able to address a wide range of cancers was commissioned at the Loma Linda University Medical Centre (LLUMC) in Loma Linda, California. However, the cost, size, and complexity of proton therapy systems greatly limited their widespread clinical use. By 2010 these facilities were joined by an additional seven regional hospital-based proton therapy centres in the United States, and many more worldwide. The number of these centres is rapidly growing with about 60 presently treating patients for prostate cancer and another 5 likely to start treating patients by the end of 2020. At least another 12 centres are in the advanced planning stage. See my web site at www.anabcofprostatecancer.com.au for a comprehensive list of world-wide proton therapy centres together with their contact details. (See Appendix 5 for the names of existing and planned centres). A number of additional centres exist that only have a fixed beam system used exclusively for ocular, and other head cancers. This escalation in the demand for proton beam treatment facilities has been fired by the ability of the technology to treat patients with otherwise untreatable cancers (brain stem, etc.); for treatments that limit potentially serious treatment side affects (secondary cancer formation, etc.) and improved lifestyle outcomes.

The use of PBT is due to accelerate even further following commencement of the installation of the next generation of systems that are far cheaper to buy, install and run; requiring far less physical space and radiation shielding. They also incorporate additional technological capabilities over some earlier systems. The cost of these new ‘compact’ systems is typically in the order of US$40 - $80 million versus US$150 - $250 million for the larger systems, which are truly huge in size. Gantries require a three-story building in which to house them, with two stories typically below ground level to offer increased radiation shielding.

Latest Developments in Proton Therapy

The Holy Grail for the radiation oncologist is the ability to deliver the maximum dose of radiation to the malignant tumour, while limiting damage to healthy surrounding tissue. Easily expressed, but it is very challenging to deliver in practice. Proton beam therapy gets very close to meeting this goal. A successful research project at a leading physics research institute in Switzerland, almost 12 years ago, made a giant step towards reaching the Holy Grail, when they announced a new procedure called the Spot-Scanning technique. This dynamic, 3-D conforming radiation therapy procedure made it possible for a higher radiation dose to be applied to a tumour, with reduced damage to the surrounding healthy tissue for most of the irradiated tumours. This technique is now more generally known as Pencil Beam Scanning (PBS). It allows a charged-particle beam, with particular properties (intensity, size, position, etc.) to be positioned very precisely at any desired spot within a tumour for a specified time and energy level. The technique allows numerous spots to be irradiated. Each spot is individually monitored to ensure the desired radiation dose is applied uniformly within the tumour. This extremely precise and homogeneous irradiation provides outstanding results, considering the generally irregular shape of tumours. Pencil Beam Scanning is likely to be a feature in all new systems being installed worldwide.

To date only a few facilities, have PBS capability to treat prostate cancer, including the MD Anderson Proton Therapy Centre in Texas. Their complex treatment planning systems and an intricate set of magnets focus a narrow proton beam and essentially ‘paint’ a radiation dose layer by layer. This leaves healthy tissue and other adjacent critical areas of the body unharmed. This Centre also pioneered the introduction of intensity-modulated proton therapy (IMPT) which they use to treat complex or concave tumours adjacent to the spinal cord or head and throat locations.

The availability of the new generation of ‘compact’ proton beam systems sees them being installed by private radiation groups. They are also placed in facilities with little space or access to the huge capital sums needed to install multi-gantry systems. This can only put downward pressure on the costs of undertaking proton therapy. Another outcome is that this therapy is becoming more ‘main-stream’ with the result that an increasing number of health insurers are likely to cover the cost of this form of cancer treatment as the costs decline. The escalation in the number of cancer treatment centres, which have proton beam therapy systems, will put a stop to the view that proton therapy is an experimental treatment and allow this treatment modality to become a truly ‘mainstream’ treatment in the eyes of all.

What radiation dose might be needed?

Radiation oncologists refer to nominal radiation and effective biological doses which are both measured in Gray (Gy). The biological effective dose also takes into account how the dose was deposited. A typical therapy dose for the destruction of a tumour is approximately 60 to 78 Gy.

Dr Cho, who was responsible for my treatment at the National Cancer Centre, Seoul, South Korea replied to my post-treatment query regarding the dosage I had received, confirming that the biological effective dose is all important. He went on to say:

“You have definitely received a less nominal total dose of 7000 cGy delivered in

28 fractions over 5.5 weeks instead of 7800 cGy in 39 fractions over 8 weeks. However, the biological effective doses (which are more important than the nominal doses) are about the same between these two dose levels. If 7800 cGy are delivered within 5.5 weeks (279 cGy x 28 fractions) instead of 8 weeks, it will be too toxic to tolerate. Considering the recovery mechanism of the human body, we have to adjust the total dose depending on overall treatment time, 5.5 weeks vs. 8 weeks. In summary, 7000 cGy/28 fractions/5.5 weeks are equivalent to 7800 cGy/39 fractions/8 weeks in terms of biological effectiveness."

By way of background, I opted for the 28-fraction treatment rather than their standard treatment of 39 fractions usually offered to international prostate cancer patients, due to a time constraint I had back in Australia. Interestingly, most Korean prostate cancer patients undergo the 28-fraction regime.

Interestingly, the Journal of Clinical Oncology 37, no. 7_suppl (March 1 2019) 80-80., published an article titled "Four-year outcomes of hypo fractionated proton therapy (HFPT) for localized prostate cancer," by Amardeep S., et al. It reported on 184 men who had 70Gy over 28 fractions. The study concluded that HFPT is associated with low rates of toxicity in the treatment of prostate cancer. Further analyses are warranted to assess long term toxicity and understand differences between proton and photon HFRT.

Why choose proton therapy?

Undoubtedly, the chief advantage of proton beam therapy over other radiation treatments for prostate cancer lies in its ability to direct high energy radiation to the tumour alone, whilst minimising the exposure of healthy tissue to this potentially damaging high radiation dose. This minimizes the risk of impotence, and incontinence and also lessons the risk and severity of rectal burning/bleeding.

What does the literature tell us?

It has been shown that higher doses of radiation therapy provide better outcomes in extending the percentage of patients who remain recurrence free of prostate cancer.[21],[22] It is generally considered that proton beam treatment, in which high doses of radiation can be focussed specifically on the tumour, yield good outcomes.[23] Its ability to escalate the dose, in some instances, has been shown to achieve a higher probability of ‘cure’ than conventional radiotherapy. These include ocular tumours, skull base and spinal column tumours and inoperable sarcomas.[24]

There is another class of treatment (which includes paediatric and prostate cancers) where the increased precision of proton therapy is used to reduce unwanted side effects, by limiting the dose to normal tissue. In these cases, patients are prescribed similar proton radiation doses to those used in conventional radiation therapy, with similar clinical outcomes being achieved. There is convincing clinical data that demonstrate the advantage of sparing developing organs in children by using protons. This minimizes the exposure of healthy tissue to radiation, and results in less long-term damage to the child. Conventional radiotherapy can affect normal growth in children with cancer.[25]

A historical review of actual patients treated with proton beam therapy or x-rays at Harvard to judge the risk of secondary malignancies from the radiation treatment was concluded in 2008. The study authors reported that there was a 50% lower risk of developing a secondary malignancy among patients treated with PBT versus x-rays.[26] A further study found that proton therapy reduced the risk of a secondary cancer by 26% to 39% compared to IMRT.[27]

In 2007, a Proton Task Force of the American Society of Radiation Oncology (ASTRO) was assembled to evaluate PBT. This body reported its findings in April 2012 after reviewing all pertinent data up until November 2009. It reviewed a host of cancer types treated by PBT including prostate cancer. It concluded “Current data do not provide sufficient evidence to recommend PBT in lung cancer, head and neck cancer, GI malignancies (which includes prostate cancer), and paediatric non-CNS malignancies.” It further concluded that “In paediatric CNS malignancies PBT appears superior to photon approaches, but more data is needed.” [28]

There are a number of studies that suggest that the apparent small benefits of PBT might be the result of inconsistent patient set-up and internal organ movement during treatment. These two circumstances may offset the PBT advantage of increased precision. (My experience at the National Cancer Centre in Seoul suggests that patient set up was very precise. Some ten minutes were taken to set the beam entry position (via each hip) using x-ray evaluation in two planes (above and from the side) with these images superimposed on a stored CT scan image. This protocol ensured that for each treatment, I was physically in exactly the same position to within millimetre accuracy. I also had to endure the placement of a condom covered probe up the rectum before each treatment, with this ‘device’ inflated with water to press the prostate forward into a reproducible position each day. This 10 second procedure was a little challenging the first time I underwent it, but became much less so, (except for the one occasion when a new therapist under training did his first live insertion of the device).

The ‘The Wall Street Journal’ of 13 December 2013, reported the findings of a study published in the Journal of the National Cancer Institute that proton beam therapy provided no long-term benefit over traditional radiation despite far higher costs. The data for the study came from an analysis of 30,000 Medicare (USA) beneficiaries. These findings have added to the heated debate among urologists, radiation oncologists and health-care administrators as to the cost to benefit of proton beam therapy versus standard radiation therapies or surgery. The main debate has been over ongoing side effects of the various treatment modalities.

Several major US proton centres, led by the Massachusetts General Hospital and University of Pennsylvania, in 2012 launched a Phase 3 randomized trial of

IMRT vs PBT for localized low and low-intermediate risk prostate cancer, with the following primary outcome to be measured at 24 months following radiation:

Efficacy of PBT vs. IMRT

Compare the reduction in mean EPIC bowel scores for men with low or low-intermediate risk prostate cancer treated with PBT versus IMRT (where higher scores represent better outcomes).

The secondary outcomes to be measured at 24 months after radiation was concluded are:

Disease Specific Quality of Life (Assess the effectiveness of PBT versus IMRT for men with low or low-intermediate risk prostate cancer in terms of disease-specific quality of life as measured by patient-reported outcomes, perceptions of care and adverse events).

Cost Effectiveness of PBT versus IMRT (Assess the cost-effectiveness of PBT versus IMRT under current conditions and model future cost-effectiveness for alternative treatment delivery and cost scenarios).

Radiation Dose and Bowel, Urinary and Erectile Function (Develop predictive models to examine the associations between selected metrics of individual radiation dose distributions and patient reported bowel, urinary and erectile function.

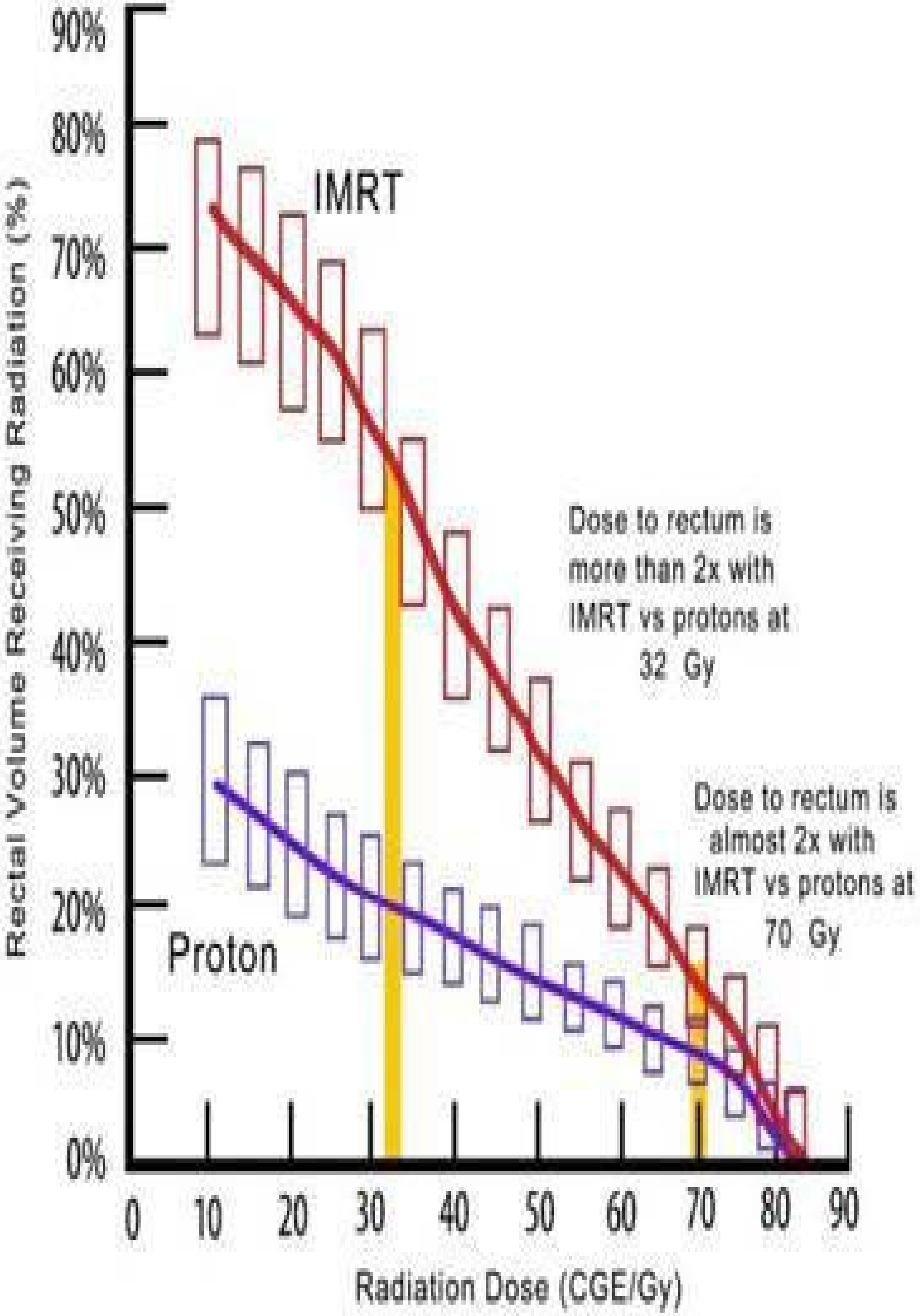
Identification and Evaluation Biomarkers of prostate cancer behaviour (Identify and evaluate biomarkers of prostate cancer behaviour and response to radiotherapy).

Long Term Survival (Assess longer-term – 10 year) rates of disease-specific and overall survival as well as development of lasting effects such as second cancers.

The study was to report in 2017 with its findings eagerly awaited by the medical profession. Sadly, the study has had difficulties in recruiting sufficient ‘paying’ participants and has now merged with the Phase 3 PARTIQoL randomized controlled clinical trial, which will conclude its 400 men recruitment by early 2020. One benefit in the delay will allow it to also report on the outcomes of patients receiving PBT treatment using pencil beam scanning and other PBT innovations provided by the newer ‘second-generation' PBT’s, which have only recently been introduced. At least 19 US PBT centres are participating in the trial, in which men can select PBT or IMRT.

A paper titled “Proton beam therapy and localized prostate cancer: current status and controversies,” by J. A. Efstathiou et al., reviews the position of proton beam versus other radiographic treatments very thoroughly.[29] You can access it via Appendix 3 later in the book. Another interesting statistic is the extent to which PBT centres allocate their treatment slots to prostate cancer versus other conditions. A 2004 analysis concluded that 26% of treatments at proton beam centres worldwide were for prostate cancer. Some individual centres have reported their prostate cancer time slots to be around half of those available or slightly higher.

The dose/volume graph, that follows, demonstrates the dose to the rectum with prostate radiation; the red colour illustrates the excess radiation dose deposited in the rectal wall with x-rays versus PBT; (35% less dose to the bladder, 59% less dose to the rectum).[30]


90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Rectal Volume Receiving Radiation (%)
IMRT
Proton
Dose to rectum is
more than 2x with
IMRT vs protons at
32 Gy
Dose to rectum is
almost 2x with
IMRT vs protons at
70 Gy
0
10
20
30
40
50
60
70
80
90
Radiation Dose (CGE/Gy)

Radiation Dose to the Rectum: PBT vs. X-ray

Image: Courtesy of the University of Florida

Use of the hydrogel SpaceOAR® (referred to earlier in the book) would substantially reduce the possibility of rectal damage by any proton or photon-based radiation treatment. This product is still not available in many countries, but as its availability increases, it will become a regular addition to many radiation protocols.

Some facilities using the hydrogel spacer have found it possible to stop using the rectal water balloon, which is used for precise positioning of the prostate gland. Hurrah! The next step in image guidance for proton therapy is the use of a cone-beam CT. MGH has purchased a cone-beam x-ray for installation on their PBT system, which may help address minor beam path uncertainty. To improve beam accuracy further at the Mayo PBT centres, prostate cancer patients now have 4 carbon fiducial markers implanted in the prostate prior to treatment. More improvements in PBT delivery are likely.

What possible questions should I ask my Specialist about proton beam radiation therapy?

(In some countries there are no or few PBT treatment centres. Thus, it is highly likely that many doctors and specialists (urologists, oncologists or radiologists included) will not be fully or even partially familiar with proton beam radiation, so bear this in mind when you review the possible questions below. Some questions might be appropriate and others might not be at all relevant dependant on the knowledge and experience of the doctor as far as PBT is concerned).

Are you familiar with the technique of PBT?

Do you have any experience as regards PBT? If yes, how many of your patients have had PBT? What were their outcomes? Were the outcomes better than IMRT, worse than IMRT or were they about the same?

What short-term side effects did they experience?

What longer term side effects did they experience as regards erectile dysfunction, incontinence and rectal bleeding? Are there any other lasting side effects?

Were any of these patients treated on a PBT system that included Pencil Beam Scanning?

If so, were their outcomes different to those treated by IMRT? By other PBT systems?

How many radiation sessions will I need?

What can I do to prepare myself for the radiation treatment?

What can I do to speed my recovery?

If you don’t recommend PBT or have no specialised knowledge of the technique, is there someone you could recommend me to? Are they local? Are they overseas?

Should I get a second opinion about possible PBT? If not, why not?

Do you use or recommend SpaceOAR® hydrogel so as to lessen or avoid radiation damage to the rectum?

If there is a future recurrence of the cancer, what ‘salvage’ treatments are available?

Is there a prostate cancer support group that you might recommend?

Am I likely to get as good an outcome as: surgery; brachytherapy (both types), other treatments?

What will the radiation sessions cost? What percentage will be covered by Medicare? What percentage will be covered by my private health insurance? What percentage will I have to bear out of my own pocket?

What if I have had previous prostate surgery, TURP or bladder neck incision?

Will I still be able to father children after the radiation session?

After the radiation treatment is complete, what is the follow up procedure? Short-term? Longer term?

Summary – Proton Beam Therapy

Proton therapy is an external-beam radiation therapy technique not dissimilar to conventional high energy x-rays used in EBRT and IMRT systems. The difference is that protons are heavy charged particles that deposit their radiation dose in a very precise targeted manner. When protons enter the body, they have little lateral scatter in the body tissue with the beam hardly broadening.

The effectiveness of proton therapy is found in the ability of the protons to deposit almost all of their energy at a specific depth (the Bragg Peak Effect). Precisely within the tumour (or overall prostate), not before or after it, as is the case with the x-ray radiation methods.

Pencil beam scanning allows very precise delivery of the energy of the proton beam, to very small targets with the energy being released at specific depths. A single treatment might see the required dosage delivered uniformly to the target area and depth by a large number of overlapping ‘sub-beams’.

Some Factors in favour of PBT

Radiation exposure to the bladder and rectum were found in a University of

Florida study to be 35% and 59% lower respectively, for PBT versus IMRT.

Less healthy tissue is impacted by PBT.

Systems with pencil beam scanning capability provide further improved control and delivery of the energy beam to the target than ‘standard’ PBT systems.

Generally, less risk of impotence and incontinence compared to other radiation treatments.

Some Factors against PBT

The high cost of treatment is prohibitive to most people who don’t have the treatment cost substantially or fully covered by a health fund.

With relatively few PBT facilities around the world, the patient might be away from home for 7 to 11 weeks and incur significant accommodation and travel costs.

Like all forms of radiation treatment, salvage procedures are compromised somewhat, should there be a recurrence of the cancer in future years.

Image: The author with the National Cancer Centre radiation technologists in the gantry room which was ‘my home’ for 30 minutes each weekday whilst in South Korea.

8.5. Low Dose Rate Brachytherapy (Seeds)

Brachytherapy is a form of prostate cancer treatment in which ionizing radiation is delivered via radioactive material placed a short distance from, or within, the tumour. The unusual name for the procedure is derived from the Greek word brachys which means brief or short. There are two formats of brachytherapy. One (low dose rate brachytherapy) involves the ultrasound and template-guided insertion of radioactive seeds into the gland. The other (high dose rate brachytherapy) involves the short-term insertion of radioactive needles or rods into the prostate gland with a repeat treatment generally done within 12 hours.

Seed brachytherapy partially went out of vogue 20 or 30 years ago, mainly due to the imprecise placement of the radioactive seeds into the prostate, clinician radiation exposure, etc. Other reasons were the improved performance of external radiation beam treatment (EBRT) and improvements in nerve-sparing technique in prostatectomy. The early 1990’s saw introduction of improved transrectal ultrasonography (TRUS) together with the development of a guidance template that led to the introduction of percutaneous brachytherapy for the treatment of localized prostate cancer. This technique offered a significant advantage over EBRT in allowing higher radiation doses to the prostate with the benefit of reduced recurrence of prostate cancer over time.

The seeds that are implanted are about the size of a grain of rice with the number being implanted being dependant on the size of the prostate gland (and other factors). Typically, 60 to 120 seeds are permanently inserted in the prostate. These seeds are inserted through the skin between the scrotum and the anus using 20 or more needles via a template. Before the procedure, the specialist will plan the positioning of the seeds in the prostate to ensure all cancerous areas are in immediate proximity to the radioactive seeds. The procedure is generally done under general anaesthetic and requires an overnight stay in hospital.

Patients undergoing LDR brachytherapy should have a prostate size of less than 60 cc (ml). If the prostate is larger, it is possible that areas of the gland are shielded by the pelvic bones, thus reducing the effectiveness of the radiation. In some instances, patients with prostate volumes of greater than 60cc, undergo hormone therapy for three months to reduce the size of the prostate to a size more suited to LDR brachytherapy. Patients with strong evidence (from biopsy results) that the cancer is fully contained within the prostate and meet low risk criteria (stage T1-T2a cancer; PSA 10 ng/ml or less and a Gleason score of 6 or less) are treated with brachytherapy alone (monotherapy). Typical prescription doses for monotherapy are 145 Gray for iodine (I)-125 and 120-125 Gray for palladium (Pd)-103.

Brachytherapy candidates where there is a high risk that the cancer has migrated from the prostate or who have at least two of the following criteria (stage higher than T2a cancer; PSA greater than 10 ng/ml and a Gleason score of 7 or higher) should undergo supplementary radiation by IMRT. Many urologists err on the side of conservatism, by recommending intermediate risk candidates to also undergo supplementary radiation.

Cancer cells grow by dividing much more quickly than normal cells. This rapid increase in cancer cells makes them most susceptible to the effects of radiation. Therefore, the radiation released from the brachytherapy seeds will kill the rapidly-dividing cancer cells. Healthy cells will be less affected by the radiation emitted by the seeds.

The isotopes most commonly used for permanent implanted seeds are iridium (Ir)-192, iodine (I)-125 and palladium (Pd)-103, which have half-lives of 74, 59 and 17 days respectively. It is thus important that the patient should not hold babies or young children on their laps for three to four months after the seeds have been inserted, because of the radiation exposure to children. Similarly, close proximity to pregnant women should also be minimised. Iridium (Ir)-192 delivers higher dosages of radiation than the other radio isotopes noted above. All three isotope seeds lose all their effective radiation within less than nine months after insertion.

The advantages of low dose brachytherapy are:

It’s a minimally invasive one-off procedure.

It offers lower risk of impotence, urinary incontinence and bowel problems.

Patients are usually able to return to their normal activities within a few days.

The disadvantages are:

A need to screen your urine for two weeks after the procedure, to ‘capture’ any seeds that may migrate into the urethra.

The possibility of the seeds migrating to elsewhere in the body, e.g. the lungs.

Possibility of a need to have a urinary catheter in place for up to a few weeks after the procedure (In as many as a reported 15% of cases).

Urinary urgency and increased frequency.

Potential impact on social and family interactions as mentioned above.

Other side effects are:

Short-term

Bruising and soreness between the legs where the needles have entered the body.

Blood in urine and semen.

A feeling of constipation due to swelling of the prostate or conversely, a feeling of a need to open one’s bowels.

All these generally pass after a few weeks.

Longer Term

Some rectal bleeding occurs due to inflammation of the rectum (proctitis) in about 2% of patients.

Narrowing of the urethra sometimes occurs, somewhat restricting urinary flow.

(A good web site on LDR brachytherapy is accessible via Appendix 3).

The Prostate Cancer Results Study Group (P. Grimm, et al.) was formed in the USA seven years ago to review 18,000 papers published over the period 2000 to 2010 in order to undertake a statistical comparative analysis of PSA free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by EBRT, brachytherapy and/or ADT. Their results suggested that brachytherapy provides superior outcomes in terms of biochemical-free progression for low risk patients. In intermediate risk patients, the combination of EBRT and brachytherapy appeared to be equivalent to brachytherapy alone, whereas in high-risk patients, a combination of EBRT, brachytherapy, with or without ADT, appeared to give better outcomes than mono-treatment protocols.[31]

Two advantages of seed brachytherapy are the greater sparing of the rectum brought about by the rapid reduction in the radiation dose delivered and the ability to provided higher initial dosage when compared to photon radiation techniques such as EBRT or IMRT. A further advantage is that in the years following the LDR brachytherapy as a monotherapy procedure, it is possible to have surgery or other salvage treatments.

LDR brachytherapy is performed as a two-stage technique or in real time using loose seeds. The two-stage technique, (often referred to as the ‘Seattle Technique’ after Grimm and Blasko from Seattle, who pioneered the technique in the late 1980s), is the most common technique used in the USA, the UK and many other countries. It requires two clinic visits and anaesthetic; the first being a pre-planning visit, with the second visit being for the actual implant procedure. It provides excellent disease-free survival data at 12 years, with outcomes comparable to surgery. In about 2000, Louis Potters, of the New York Prostate Institute, developed his single visit intraoperative dynamic approach whilst working at Memorial Sloan Kettering Cancer Centre. This technique, known as the ‘Potters’ Approach’, is also able to treat larger prostates (due to less pubic arch interference). The Potters’ Approach provides better control and flexibility for seed placement to that previously available. It also provides better dosimetry outcomes as well as minimising radiation exposure to the urethra and the rectum. Patients have minimal discomfort and a rapid return to normal activity. This highlights the benefits provided by LDR brachytherapy when compared with more ‘radical’ treatments.

In January 2012, an article by Stephen E. M. Langley and Robert W. Laing was published which outlined a new real-time prostate brachytherapy technique using stranded and loose seeds.[32] Use of the 4D Brachytherapy protocol (as it is called) sees a combination of stranded seeds inserted around the periphery of the prostate gland and loose seeds placed within the centre of the prostate in a single stage real time process. A standard ultrasound scan, together with a web-based nomogram allows the number of stranded and loose seeds required for the procedure, to be determined. The procedure, performed by two clinicians working together, is usually completed in less than 45 minutes (compared with 60 to 120 minutes for a two-stage procedure). It provides better dosimetry and clinical outcomes with lesser side effects in comparison with the more common two stage protocols used. (It is interesting to note that the above two doctors, were in Hobart, Australia in March 2016, to train local specialists in their 4D Brachytherapy technique).

The use of stranded seeds (in most LDR brachytherapy procedures) reduces the risk of their migration from the prostate gland to elsewhere in the body. The placement of loose seeds in the centre of the prostate gland optimises the radioactive dose to cancerous areas of the prostate whilst minimising the radiation to tissue surrounding the prostate. Stranded seeds are woven into a strand of absorbable material to help maintain their position. It is likely that x-rays will be taken during the implant procedure to check on their precise position of the inserted seeds. A CT scan is also likely after the procedure has been completed. In most instances, the patient is provided with a course of medication to be taken for a period after the procedure. These might include an alpha blocker such as Tamsulosin (Flomax®) which helps to relax the swollen muscles of the prostate, reduces pressure on the urethra and improves urinary flow. Additionally, an anti-inflammatory painkiller may be prescribed that again reduces inflammation and pain. An antibiotic is usually also taken to minimise the chances of infection. After the procedure it is likely that the patient will have some urinary retention in the form of an almost constant desire to urinate and an inability to do so. This in turn causes abdominal discomfort. Most clinics teach the patient to catheterise themselves using sterile disposable catheters, thus avoiding return visits to the clinic or their GP. Within a few weeks the urination difficulty is like to reduce and the need for catheterisation will pass.

Research suggests that erectile dysfunction will occur in about 20% of patients undergoing LDR brachytherapy. It is reported that about 80% of these cases respond very well to Viagra or similar medication. About 10% of patients experience minor bowel problems such as urgency and/or diarrhoea. These usually dissipate within a month or so of the insertion of the seeds.

There is another form of brachy (other than LD and HD brachytherapy) which is brachy BOOST therapy. It is only used when the cancer has spread to local lymph nodes (N1 stage). It is different to the two common brachy forms and is delivered by a radiation oncologist with specific skills in brachy BOOST therapy delivery. The therapy consists of external beam radiation to the whole pelvis and a boost of brachytherapy to the prostate itself. The literature suggests that this therapy is often curative. For men with cancerous lymph nodes, 2-3 years of ADT are generally given as a follow up.

Isoray Inc., a US medical technology innovator, recently announced that its brachytherapy delivery system has been used in the first prostate cancer surgery at the Hollings Cancer Centre at the Medical University of South Carolina. Their Build-Blu delivery system is a disposable, next-generation, seed-stranding device that will allow prostate brachytherapists to affordably build custom-configured strands with Cesium-131 in the operating room, thereby allowing clinicians to individualize the procedure to the patient’s anatomy in real time. It is one of the first new products to emerge in the brachytherapy field in quite some time.

What is PSA Bounce?

PSA levels decline to about 0.5 ng/ml over a period of some months after a successful seed implant, with some variability from patient to patient. Some patients, after the initial fall in PSA value, experience a rise in their PSA some 1 to 2 years after a successful seed implant. This increase is seen in up to 30% of cases with the increase in PSA value usually being in the 0.5 – 1.5 ng/ml range. In rare cases, it may rise to higher than 10 ng/ml. This phenomenon is referred to as PSA Bounce and is not preventable. Its occurrence does not suggest a poorer outcome from the seed implant procedure. The reason for a PSA Bounce occurring does not appear to be fully understood.

What Questions should I ask my Specialist about LDR Brachytherapy?

Could my prostate be too big to do a seed implant?

Will I need hormone treatment before the implant? If yes, why? If not, why not?

Will I require external beam radiotherapy as well as brachytherapy?

How long does the procedure take? How long will I be in hospital?

How many of these procedures do you do a year?

How will I know if the implant is likely to be successful?

What are the urinary side effects? What about retention of urine?

What are your results in respect of impotence, fertility and incontinence?

Will I have much pain after the implant?

Do I have a follow-up appointment after discharge, and when will the PSA first be measured?

Ongoing how often will my PSA be checked? How will I be followed up long term?

What should the PSA be after brachytherapy? What would it mean if it doesn't reach that level? What would you do then?

What are the rectal side effects?

What if I have had previous prostate surgery, TURP or bladder neck?

Should the cancer return at a later date what salvage treatment options would I have?

Summary – LDR Brachytherapy

Low dose rate brachytherapy involves the ultrasound and template-guided insertion of radioactive seeds into the prostate.

Typically, 60 to 120 seeds are permanently inserted in the prostate with the number inserted determined by the size of the prostate and other factors.

The seeds are inserted through the skin between the scrotum and the anus using 20 or more needles via a template. Before the procedure, the specialist will plan the positioning of the seeds in the prostate to ensure all tumours are in immediate proximity to the radioactive seeds. The procedure is generally done under general anaesthetic and requires an overnight stay in hospital.

Erectile dysfunction occurs in about 20% of cases, with these responding well to Viagra or similar medication. About 10% of patients experience short-term bowel problems such as urgency and/or diarrhoea.

Some Factors in favour of LDR Brachytherapy

It’s a minimally invasive one-off procedure.

It offers lower risk of impotence and bowel problems.

Patients are usually able to return to their normal activities within a few days.

Some Factors against LDR Brachytherapy

The possibility of the seeds migrating to elsewhere in the body, e.g. the lungs; or lost during urination or intercourse.

Possibility of a need to have a urinary catheter in place for up to a few weeks after the procedure (In as many as a reported 15% of cases).

Urinary urgency and increased frequency.

Greater risk of bladder problems compared with EBRT and HDR brachytherapy.

Low dose brachy is not as popular today, as the target men are now inclined to go onto active surveillance.

8.6. High Dose Brachytherapy

High dose rate (HDR) brachytherapy involves the short-term insertion of radioactive needles or rods into the prostate gland with a repeat treatment generally done within 12 hours. HDR brachytherapy is often referred to as temporary brachytherapy due to the radiation sources only being introduced to the prostate for short periods of time. A key attribute of HDR brachytherapy is the ability to introduce the radioactive isotope into a defined area within or immediately adjacent to the cancerous growth. This lessens the radiation damage to adjacent healthy tissue.

High-dose rate (HDR) brachytherapy is when the rate of dose delivery exceeds 12 Gy•h-1 compared to a typical LDR brachytherapy dose rate of 2 Gy•h−1. In HDR brachytherapy the radioactive needles or rods are maintained in situ in the prostate gland for a few minutes at a time. Whereas LDR seed implants are usually a monotherapy (standalone therapy), HDR brachytherapy is predominantly used in conjunction with radiotherapy, with the radiotherapy preceding or following the HDR procedure. UCLA Health in the United States has treated more than 500 patients using HDR brachytherapy as a monotherapy. Their Monotherapy HDR protocol is designed to minimize side effects by giving treatment in a series of two ‘implant’ procedures, performed approximately one week apart. Three HDR treatments (‘fractions’) are given with each implant so a total of six fractions complete the course of treatment. Patients are selected for this program being deemed unsuited to their more common HDR plus EBRT procedures due to their higher Gleason score (8-10), etc. Their protocols have been replicated throughout the world.

In patients in which there is strong evidence (from biopsy results) that the cancer is fully contained within the prostate and meet low risk criteria (stage T1-T2a cancer; PSA 10 ng/ml or less and a Gleason score of 6 or less) are likely to be treated with LDR brachytherapy alone (monotherapy). Typical prescription doses for monotherapy are 145 Gray for iodine^{125} and 120-125 Gray for palladium^{103}.

I-Chow Hsu, et al.,[33] of The American Brachytherapy Society's Prostate High-Dose Rate Task Group reported in 2008, the following inclusion criteria for patient's suited to HDR brachytherapy: Stage T1-T3b and selected stage T4; with a Gleason score of 2-10; PSA with no upper limit, but clear evidence of no metastasis beyond the prostate (TxN0M0). Exclusion criteria included severe urinary obstructive symptoms, extensive TURP defect or TURP within 6 month and/or collagen vascular disease. Patients not able to lie flat or unable to undergo anaesthesia (general, spinal, epidural, or local) were also excluded. Patients with Stage T1b-T2b and Gleason score ≤ 7 and PSA ≤ 10 ng/ml were suggested to be suited to Monotherapy (HDR alone) with prescriptive doses of 10.5 Gy for each of three exposure sessions; 8.5-9.5 Gy for each of four exposures or 6.0-7.5 Gy for 6 sessions. The Task Group recommended that those receiving HDR brachytherapy as a Boost therapy to radiation therapy (EBRT; IMRT; etc.) would receive 15 Gy for a single exposure and with 36-40 Gy of x-ray therapy (XRT); 9.5-10.5 Gy for two exposures (with 40-50 Gy XRT); 5.5-7.5 Gy for three exposures (with 40-50 Gy XRT) or 4.0-6.0 Gy for 4 HDR exposures (with 36-50 Gy XRT).

The Task Force also recommended the following post treatment follow up protocol:

Serial PSA measurements – baseline at 3-6 months and then every 3-6months and/or per institutional protocol.

Quality of life assessment - Urinary, bowel and sexual function should be prospectively assessed.

Post-Treatment biopsy - Should be reserved for protocol settings or in clinical situation where salvage local therapy is being considered.

HDR brachytherapy has a few minor advantages over LDR brachytherapy, in that no radioactive sources remain in the body after treatment. Therefore, there is no radiation risk to friends or family from being in close proximity to the patient. There is no chance of passing a seed into a partner via intercourse or of migration of radioactive seeds into other organs of the body (e.g. lungs) as can occur (very infrequently) after LDR brachytherapy. The practice of HDR brachytherapy is a multi-stage procedure. It starts with the initial planning assessment in which the characteristics of the tumour are determined. The prostate is imaged via one or more modalities such as a CT scan; MRI, ultrasound or x-ray radiography. The data produced from imaging is used to create a 3D image of the tumour and its surrounding tissue. A radiation plan is then developed to determine the position of the applicators (needles or plastic catheters that contain the isotopes) to ensure no ‘cold’ spots or ‘hot’ spots in the target area. Once additional imaging has determined the correct positioning of the applicators, further aspects of the treatment plan are concluded. The images of the patient with the applicators in situ are imported into treatment planning software. The software enables multiple 2D images of the treatment site to be translated into a 3D ‘virtual patient’, within which the position of the applicators can be defined. The spatial relationships between the applicators, the treatment site and the surrounding healthy tissues within this ‘virtual patient’ are a copy of the relationships in the actual patient. The treatment planning software allows virtual radiation sources to be placed within the virtual patient. The software displays a graphical representation of the distribution of the irradiation. This allows the brachytherapy team to adjust their irradiation plan before radiation insertion begins.

The radiation sources are inserted into the applicators by a process called ‘after-loading’. Today after-loading is generally achieved via an automated system that protects the clinicians from radiation exposure. This is achieved by initially housing the radioactive sources in a shielded safe. Once the applicators are correctly positioned in the patient, they are connected to a ‘HDR remote after-loader’ machine (containing the radioactive sources) through a series of connecting guide tubes. The treatment plan is sent to the after-loader, which then controls the delivery of the sources along the guide tubes into the pre-specified positions within the applicator. This process is fully automated which allows staff to leave the treatment room. The sources remain in place for a pre-specified length of time (usually 2 to 5 minutes), again following the treatment plan, following which they are returned along the tubes to the after-loader.

The applicators are removed and the patient is transferred to the recovery ward. If a second session is planned, the applicators and the template through which the applicators pass, is maintained in situ for the second session which is not done under anaesthetic and is painless. Generally, a second session starts about 6 hours after the first session is completed. It is necessary for the patient to lie still on their back over this period to avoid moving the applicators and template in the perineum area. It is an uncomfortable and somewhat painful wait before the second (or in some instances a third) session. A Foleys catheter (for urine drainage) remains in place until the applicators and template are removed. The computer-controlled system allows the clinician/radiation oncologist to control the radiation dose in different regions of the prostate. This allows the tumour to receive a higher dose with lower dosages delivered to the urethra and the area adjacent to the rectum.

The advantages of high dose brachytherapy (without follow up radiotherapy) are:

It’s a minimally invasive one-off procedure

It offers lower risk of impotence, urinary incontinence and bowel problems

Patients are usually able to return to their normal activities within a few days

The ability to modify the dose after the needles are in place is a significant advantage of HDR over LDR brachytherapy.

With a follow up boost of radiotherapy, the number of sessions is generally less than for radiotherapy alone, which sees less radiation exposure to healthy tissue. In some instances, in both forms of brachytherapy, the radiation oncologist may also recommend short-term hormonal ablation therapy, which begins three months before the brachytherapy and continues for 3 - 12 months afterwards. This therapy consists of a quarterly injection of Lupron® or Zoladex®, and an anti-androgen medication like Casodex®. The hormone therapy will shrink the cancer, shrink the prostate gland, and reduce the PSA level. The likely result being there will be less cancer cells for the radiation treatment to destroy.

What Questions should I ask my Specialist about HDR Brachytherapy?

The questions are general the same as for LDR Brachytherapy, but with a few exceptions.

Could my prostate be too big to do HDR brachytherapy?

Will I need hormone treatment before the implant? If yes why? If not, why not?

Will I require external beam radiotherapy as well as brachytherapy?

If so, how long after the brachytherapy should radiotherapy begin?

How many treatments (or fractions as they are known) of radiotherapy are needed?

How long does the brachytherapy procedure take? How long will I be in hospital?

How many of these procedures do you do a year?

How will I know if the treatment is likely to be successful?

What are the urinary side effects? What about retention of urine?

What are your results in respect of impotence, fertility and incontinence?

Will I have much pain after the implant?

Do I have a follow-up appointment after discharge, and when will the PSA first be measured?

Ongoing how often will my PSA be checked? How will I be followed up long term?

What should the PSA level be after brachytherapy? What would it mean if it doesn’t reach that level? What would you do then?

What are the rectal side effects?

What if I have had previous prostate surgery, TURP or bladder neck incision?

Should the cancer return at a later date what salvage treatment options would I have?

Summary – HDR Brachytherapy

High dose rate (HDR) brachytherapy involves the short-term insertion of radioactive needles or rods into the prostate gland with a repeat treatment generally done within 12 hours.

A key attribute of HDR brachytherapy is the ability to introduce the radioactive isotope into a defined area within or immediately adjacent to the cancerous growth. This lessens the radiation damage to adjacent healthy tissue.

HDR brachytherapy is predominantly used in conjunction with radiotherapy, with the radiotherapy preceding or following the HDR procedure.

Some Factors in favour of HDR Brachytherapy

No radioactive source remains in the body after the procedure is completed.

As a monotherapy, it offers the shortest course of treatment.

As a combined therapy, a shorter course of EBRT (or similar) is required before or generally after the procedure.

Provides excellent radiation coverage of any microscopic extension of the cancer immediately beyond the prostate.

Minimizes areas of radiation overdose (hot spots) or underdose (cold spots) within the prostate.

A key advantage of combined HDR brachytherapy over a course of EBRT without HDR, is it offers superior control of the distribution of radiation within and around the prostate.

Radiation control rates are correspondingly high and complication rates low with HDR brachytherapy.

As a monotherapy, it is used as a salvage treatment after cancer recurrence.

Some Factors against HDR Brachytherapy

Between 50% and 67% of patients experience dysuria, urinary urgency and/or urinary retention. These conditions generally reduce over time sometimes needing medicinal support.

Erectile dysfunction has been reported in 16% of cases.

Urinary stress incontinence and urethral stricture have been reported in less than 5% of HDR monotherapy cases.

Unsuitable for men with a prostate volume of more than 60 ml due to the physical inability to reach all affected areas.

8.7 Radioactive Ligand Therapy (^{177}Lu PSMA Therapy)

Radioactive Ligand Therapy (RLT) offers significant hope for men with advanced metastatic prostate cancer that is no longer responding to other treatment regimes. I have almost first-hand knowledge of this treatment as my 79-year-old brother underwent this treatment in Sydney, starting about 24 months ago. Until September 19, his PSA was almost zero and he was lesion-free in June 19 (as shown by PSMA PET scan). In October and November 19, his PSA went from 100 to 315. Some men who had the same therapy at the same hospital have seen subsequent disease progression. See more details on the following pages.

Radioactive Ligand Therapy is also known under several different names including PSMA Theranostics, PSMA Lutetium-177 Therapy, (sometimes designated as ^{177}Lu PSMA Therapy), PSMA Radionucleotide Therapy or Peptide Receptor Radionucleotide Therapy (PRRT). In most medical jurisdictions around the world, the technique it has not yet reached clinical approval. It is therefore mostly offered to patients as a salvage therapy. However, an increasing number of clinical trials in the USA, Australia, Germany and the United Kingdom, have recruited participants or are in the process of doing so. It is certain that in the months ahead, there will be further clinical trials initiated with these trials all to recruit suitable candidates. (The present therapy performed at for-profit hospitals costs between US$6,000 – US$8,000 per injection of which 2 to 6 are required – thus free entry to a clinical trial is financially beneficial assuming that one isn’t in the placebo group).

The therapy relies on the over-production of the protein prostate-specific membrane antigen (PSMA), in prostate cancer cells and the proliferation of PSMA receptors on the surface of most men’s prostate cancer cells. (PSMA is over-expressed 100-1000 times in prostate cancers, and expression is further increased in metastatic and castration-resistant carcinomas). A biochemical compound (usually a peptide) is mated with a short-life radioactive molecule (increasingly lutetium-177) that has a strong binding affinity for PSMA and has the ability to be ‘absorbed’ via the PSMA receptors into the epithelial prostate cancer cell, where it kills the cell’s DNA.

Despite its name, PSMA is not specific to the prostate gland and is expressed in other normal cells or tissue such as the salivary glands, duodenal mucosa, renal tubular cells, and some neuroendocrine cells in the colon and neoplastic cells of the kidneys and the colon.

Side effects, which are generally minimal, include mouth dryness and minor haematotoxicity (blood toxicity). A recently published study generally confirmed the safety and favourable therapy response in previous ^{177}Lu PSMA-617 studies. This study included 24 patients who received up to 2 cycles of ^{177}Lu PSMA-617. (22 patients received 2 cycles). Eight weeks after the second cycle of ^{177}Lu PSMA-617 therapy, 15 of 22 patients experienced a PSA decline compared to the baseline PSA value, of who 15 experienced a decline of more than 30% and 13 a decline of more than 50%. Relevant haematotoxicity (grade 3) occurred during the observation period (within 2 months after the last cycle) in 2 patients only. Apart from minor grade 1 or 2 haematotoxicity, the majority of patients did not have any haematotoxicity during the observation period. No kidney or liver toxicity was observed. However, I am aware of some patients similarly treated elsewhere and outside this survey, who have had higher grades of haematotoxicity, which presents patients and their clinicians with serious challenges. Calcium and other clinical chemistries should also be closely monitored.

The overall survival benefit of this therapy in comparison to historical control groups demonstrated varied but always longer survival. The excellent results achieved by ^{177}Lu, which has a half-life of 6.7 days and low-energy β-particles emission with a mean range of 0.7 mm and maximum range of 2.1 mm in soft tissue, has another benefit in that most patients go home immediately after treatment, but need to avoid close contact with others for 72 hours. (German clinics retain patients for 24-48 hours before their release). Patients have been treated with the present form of RLT for about 4 years. Thus, the jury is still out as far as any long-term health effects of this therapy.

The body needs imaging before and after the radionucleotide has been administered. This requires PET-CT imaging with the small molecule tracer ^{68}Ga-PSMA-11 (also called HBED-CC, HBED, PSMA-HBED, or Prostamedix), which demonstrates excellent resolution in men who have strong uptake of the tracer by the cancer cells’ PSMA receptors. This process identifies men with poor or no tracer uptake by the cancer cells’ PSMA receptors which finds them unsuited for RLT.

RLT is ineffective in about 10 to 15% of men. Considerable research is being done to determine why this is so and why there is a wide range of positive outcomes from this treatment. In a recent study in European Urology, scientists at The Institute of Cancer Research, London, found that testing men for faults in the DNA repair genes in their tumours could identify those most likely to respond to RLT.

They found that the amount of PSMA on the surface of cancer cells was more than four times higher in tumours where there were also faults in DNA repair genes. That means that testing for genetic faults in DNA repair genes could be used as 1st screening to select patients for PSMA-targeted treatment – followed by ^{68}Ga-PSMA-11 imaging.

The researchers believe that PSMA plays a key role in keeping the genome in cells stable – and could be produced by tumours as a survival mechanism where they have DNA repair defects. This could explain the link between DNA repair faults and high levels of PSMA.

Earlier RLT studies have shown that the third of men who do not respond to the first cycle, did respond after a further cycle. Again, we see the physiology of prostate cancers to be heterogenous, diverse and respond differently to therapy.

Operating protocols vary from hospital to hospital, but all patients need to meet blood chemistry criteria and have a kidney function scintigraph. Anaemic men might have to have a blood transfusion before the radiation is administered.
Eligibility criteria:

Dosage: A dose of 6 to 7.4 GBq ^{177}Lu-PSMA-617.

Precaution: Cooling of the salivary glands from 30 minutes before and up to 4 hours after the ^{177}Lu-PSMA-617 injection to reduce the risk of salivary glands radiation injuries.

Using urinary catheter in incontinent patients in the first 48 hours to avoid any contamination.

Injection intravenously as a slow bolus followed by 1000 mL Ringer or saline solution.

Four to more cycles of the ^{177}Lu-PSMA-617 every 6 to 8 weeks.

Not previously treated with Radium -223 (Xofigo). (Some variability in this now seems to exist).

Follow-up after therapy:

The PSMA-PET or SPECT imaging before first cycle to be repeated after the last cycle or between cycles.

Lab assays should be performed every 2 weeks: blood cell counts, creatinine, alkaline phosphatase, lactate dehydrogenase and liver panel.

Decision to pursue this therapy depending on the imaging and clinical situation.

It has been reported that ADT increases PSMA expression which in turn improves outcomes from RLT and also might improve diagnostic PSMA PET imaging or single-photon emission computed tomography (SPECT) imaging that is also used in this setting.

Initial research in the RLT field, used larger-sized peptides and other radioactive emitters like 90Yttrium. However, these larger peptides had lower absorption by PSMA cancer cells and also took longer to leave the body after the radioactive component had done its work.

Some clinical trials are using the -177Lutetium-labeled DOTAGA-based PSMA ligand which is more commonly known as I&T. Another small molecule, 177Lu-PSMA-617, is being used in ongoing clinical trials. One such Phase 2 trial at the Peter MacCallum Cancer Centre in Australia recently reported their results for 50 men with mCRPC. Most men had been treated earlier with abiraterone, enzalutamide, docetaxel and/or cabazitaxel.[34] Of the 50 treated patients, 64% achieved a PSA decline ≥50% including 22 men with a PSA decline ≥80%. PSA declines occurred in all but 2 men. In the men with a PSA decline, 22% had a

PSA decline of less than 25%. Side effects were generally reported as being mild with transient grade 1-2 dry mouth in 68% patients, grade 1/2 transient nausea in 48% patients and grade 1/2 fatigue in 36% patients. However, Grade 3/4 thrombocytopenia (blood platelet count reduction) did occur in 5 patients. Patients who had a ≥50% PSA response had a progression free survival of 8.3 months and a median overall survival of 18 months. These results were obtained after 4 cycles.

-131Iodine was used successfully in a German clinic, with more than 61% of men seeing a PSA decline ≥50% in a 25-man trial. Of the 13 patients with bone pain, 11 had moderate/ complete pain reduction.

-225Actinium - an alpha-emitting radiopharmaceutical – has also been tagged to the PSMA-617 peptide in a recent trial. Of the 38 of the 40 patients who survived at least one treatment, 63% had ≥50% PSA decline and 87% had PSA decline of any degree[35]. Xerostomia (dry mouth) was the main toxicity, which lead to the discontinuation of treatment in 4 patients. (Many men enrolling in RLT trials have already had their health seriously compromised and have very limited treatment options still available to them). Clinical trials with RLT targeting PSMA, are being announced regularly. Recent trials include the following:

PRINCE trial -^{177}Lu-PSMA-617 with pembrolizumab (NCT03658447

Testing two different doses of ^{177}Lu-PSMA-617 (NCT03042312)

Randomized Phase 3 VISION trial (at Royal Marsden Hospital) of ^{177}Lu-PSMA-617 vs. Best Supportive Care (NCT03511664)

Results from the first studies suggested that RLT would revolutionise the treatment of mCRPC and it would become in widespread usage as soon as the necessary clinical trials where successfully concluded. Months ago, evidence started to emerge that many men who had had a positive initial response to the therapy (PSA dropping to near zero and disappearance of most or all lesions), started to see a rise in their PSA and see the return of lesions after 12 to 18 months and two or more cycles of RLT. In fact, my own brother was in this category. Two cycles 18 and 16 months ago, saw almost all his 50 lesions disappear and his PSA dropped to near zero. Look forward 12 months and his PSA had risen to about 9 and a few lesions had returned. Two more cycles of RLT were administered in December 18 and February 19. By June 19 all lesions (on PSMA PET scan) had disappeared and his PSA was below 1 and still dropping. Theranostics Australia, who delivered his RLT, where very pleased with his progress with no follow up required until November 19. (It is interesting that they are researching alternative ligands and radionucleotides with a view to finding better outcomes than are presently being experienced). My brother still had the option of a return to his enzalutamide therapy, then on failure, to abiraterone acetate (it would have been better to take these compounds in reverse order as they yield longer efficacy according to research).

Until September 19, his PSA was almost zero although he had started to have lower pelvic area pain. Disappointingly, over the next 8 weeks his PSA rose to 100 and then in two further weeks to 315, then to over 800, before enzalutamide reduced it to around 500. This increase in PSA was accompanied with extreme bone metastatic pain and a deterioration in his other clinical chemistries. His medical team concluded that he should start a course of docetaxel rather than undergo another lutetium injection. Apparently, other men undergoing the same therapy at the same hospital had also seen a rapid drop off in their condition at about the same time interval after 4 or more injections. (The J591 peptide discussed below might offer almost three times OS than the J617 peptide).

(Late Update: My brother condition deteriorated in December 19 to the point he had complete leg paralysis due to spinal cord compression and all other treatment was withdrawn other than pain therapy. His hospital oncology team had rejected the compassionate use of Veyonda® (see page 348) as it is not yet

SOC or FDA approved, even though I had presented them with all the Phase 1b trial data including endorsements from prominent local oncologists.Sadly, he passed away on the 22nd January which was a peaceful release for him after the extreme trauma and pain he experienced in his last 6 weeks).

Clearly, more research is required before RLT becomes a mainstream therapy for men with life-threatening mCRPC over the next few years. Other new therapies, some not yet approved, will join with the above two ‘drugs’ (Xtandi and Zytiga), and new advances like apalutamide and darolutamide, to incrementally extend the quality-of-life and life itself of Stage 4 sufferers.

I recently became aware of Telix Pharmaceuticals Ltd, an Australian clinical-stage biopharmaceutical company, that is publically-listed on the Australian Stock Exchange (Ticker Code: TLX). The company announced that the dose escalation data of their TLX591 monoclonal antibody (lutetium-177-labeled anti-PSMA monoclonal antibody J591), had been reported in the August 19 Cancer journal. ^{177}Lu-J591 was trialled on 49 men with mCRPC, dosed (variable strengths) two weeks apart under the direction of the Weill Cornell Medical College (WCMC). The therapy was well tolerated with notably no impact on the saliva glands even at the highest dosage used. (A key drawback till now of this therapy). The highest dose used gave the largest PSA level reductions and gave significant anti-tumour effect with a median overall survival of 42.3 months (at 95% confidence level). Perhaps the most important factor out of this dose escalation study, was that excellent results (both tumour load and minimal side effects) can be had with low and declining dosages. The larger ProstACT Phase 3 trial will start recruiting 550 men over 25 sites in 1H 2020.

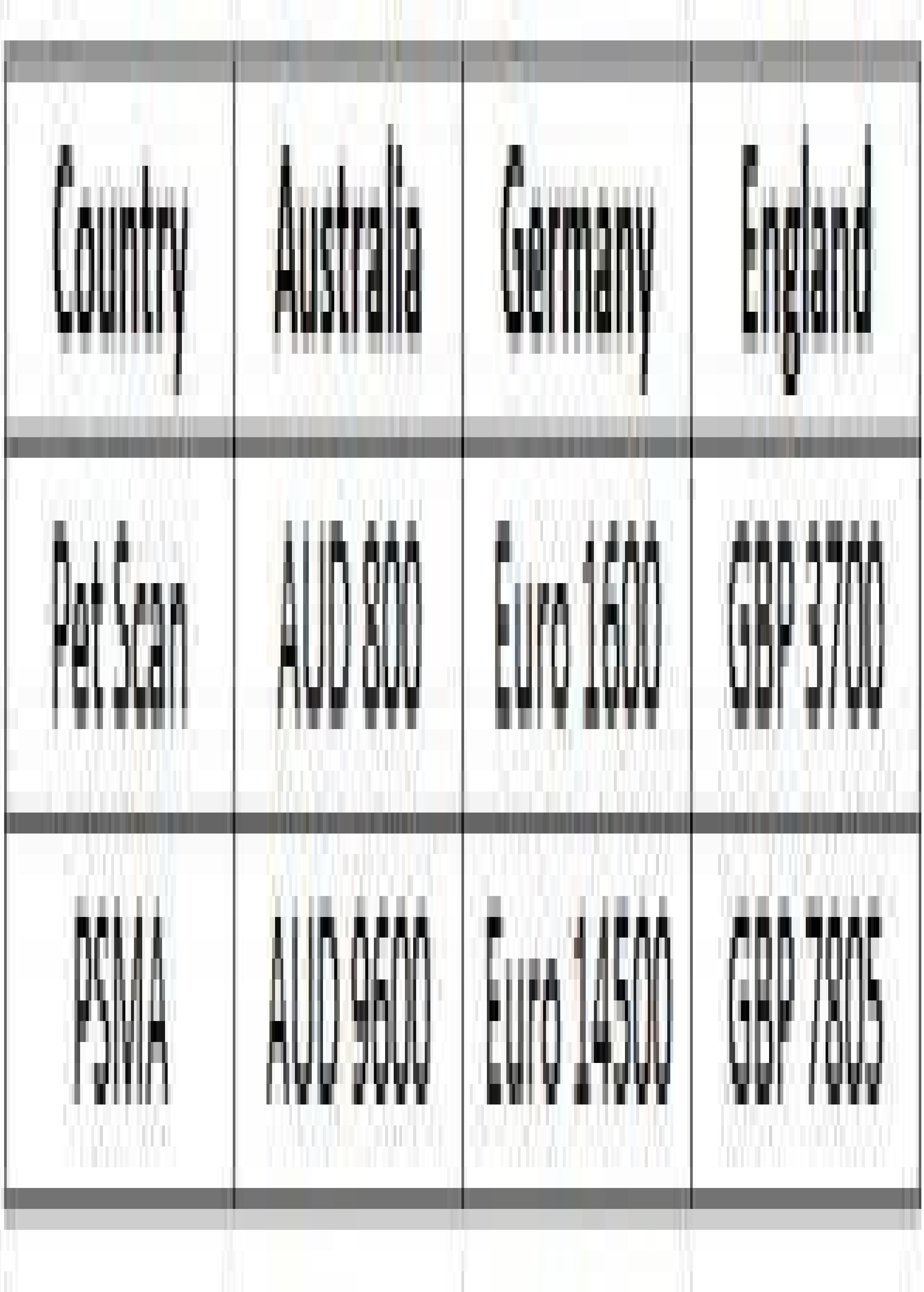
Telix also continue the development of their preparation kit (Illumet™) for ^{68}Ga-PSMA PET imaging and are in dialogue with the FDA to facilitate its future commercialisation.

In March 19, the European Association of Urology (EAU) issued their updated guidelines for the management of prostate cancer. Interesting, they included PSMA PET imaging for patients experiencing biochemical recurrence after prostatectomy. The guidelines also reflect prevailing clinical experience that PSMA PET is preferable to other imaging solutions (Axumin®, etc).

WCMC researchers reported at ASCO19, the results of their treatment of 216 men with mCRPC with PSMA-targeted radionuclide therapy, including ^{177}Lu-J591 (n = 136), ^{177}Lu-PSMA-617 (n = 38), Lu-J591 + Lu-PSMA-617 (n = 6), ^{225}Ac-J591 (n = 7), and ^{90}Y-J591 (n = 129). They found that 74.5% of the men had high PSMA expression which was associated with a significantly larger average PSA decline. Thirteen men who had no PSMA uptake still exhibited some level of PSA decline. The research re-affirmed that not all types of prostate cancer expresses the same level of PSMA. The level of PSMA expression measured by imaging is associated with the likelihood of response. However, a sub-set of patients, without any significant PSMA uptake on imaging, had a positive response to PSMA therapy. This finding has contradicted current thinking that dose uptake on imaging is the key criteria for patient selection. No comparisons were made between the different radionucleotides used.

RLT like many other cancer therapies are hugely expensive that tax health fund budgets and are beyond the reach of many families. Hopefully, the cost issue will be addressed over time, so that it might save lives regardless of one’s ability to pay.

Approximate Costs as of August 2019



Country	Australia	Germany	England
Pet Scan	AUD 800	Euro 1600	GBP 3700
PSMA	AUD 9600	Euro 14500	GBP 7805

So, what is the Future of Radioligand Therapy?

It is estimated that more than 3000 men have to date undergone RLT with ^{177}Lu-PSMA-617. Many have been paying customers in Germany, Austria and Australia. Clinicians and researchers have more and more data to peruse from clinical trials and commercial patient follow up. Almost all facilities offering RLT continue to research improvement in the therapy. Such improvements as reported in Cancer by the Weill Cornell Medical College where dosage changes have led to no damage to the saliva glands, are likely to be a frequent occurrence.

Most men treated to date have substantially been ‘treatment of last resort’ cases. It was pleasing to see the Peter MacCallum Cancer Centre (PMCC) in Melbourne, Australia, recently receive significant government funding for a clinical trial with men who have just been diagnosed with mCRPC. With lesser cancer burdens, results for this group of men will be awaited with great interest. The trial which should complete recruitment by late 2019, will compare results of treating men with ^{177} Lu-PSMA-617 plus ADT and followed by docetaxel, versus men on ADT followed by docetaxel. Another arm of the Phase 2 trial called the LuTectomy arm will see men with high activity on a PSMA PET/CT, given a single cycle of LuPSMA a few weeks prior to surgery. A repeat PSMA PET/CT will be done prior to their prostatectomy to determine if this is a successful strategy and will reduce recurrence rates.

They are also recruiting for their multi-centre LuPARP trial. This Phase 1 trial is for mCRPC men who have failed taxane chemotherapy (and/or enzalutamide and/or abiraterone and/or apalutamide) will received 7 GBq of ^{177} Lu-PSMA-617 over 4 cycles each 6 weeks apart, followed by Olaparib in six incremental doses of 50 to 300mg over 15 days. Olaparib is a PARP inhibitor used to treat men with the hereditary BARC1 or BRAC2 genes. This will be the first of many multi-therapy ^{177} Lu-PSMA-617 plus another treatment modality trials.

The PMCC, world leaders in RLT, are also in involved in the TheraP Phase 1 randomised 200 men study which will compare Lu-PSMA with the chemotherapy cabazitaxel, which is the standard treatment for mCRPC when other treatments have stopped working. Half the participants will receive Lu-PSMA and half will receive cabazitaxel.

It is interesting to note that PMCC use FDG-PET imaging in addition to ^{68}Ga-PSMA PET scans to determine patient suitability for RLT and access to their clinical trials. Men with high metastases of the liver and with other sites of FDG-discordant disease do very badly after RLT with OS of only a few months being typical.

Progenics Pharmaceuticals, Inc. (NASDAQ: PGNX), an oncology company, in October 18 announced plans to advance I-131 1095, its PSMA-targeted therapeutic, into a Phase 2 clinical study. The Canadian multicentre RCT will evaluate the efficacy and safety of I-131 1095 in combination with enzalutamide in patients with mCRPC who are PSMA-avid (active), without chemotherapy, and with disease progression after abiraterone. Vivien Wong, Ph.D., Executive Vice President Development at Progenics said: “1095 delivers a targeted radiation dose to prostate cancer cells utilizing iodine-131 as the payload. Iodine -131 is an attractive agent to use because its physical properties of longer range and higher energy could potentially improve efficacy for bulky lesions and lesions that have lower PSMA expression.” Maybe a successful trial will lead to some of the 10-15% of men presently unresponsive to RLT, become responsive to RLT.

The issue of damage to the saliva glands is receiving much research attention. An informative paper titled “Salivary Gland Toxicity of PSMA Radioligand Therapy: Relevance and Preventive Strategies” as published in the Journal of Nuclear Medicine, August 1, 2018 (vol. 59 no. 8 1172-1173) fully describes the latest ‘state-of-play.’ Meanwhile, results from the more than a dozen other clinical trials underway at present, will also be equally enlightening.

Details of the German teaching hospitals can be accessed via Appendix 3. Similarly, details of Theranostics Australia are also listed.

Summary – Radioligand Therapy

RLT together with immunology, appear to offer many mCRPC patients, as a minimum, relief from the progression of their disease for periods of six months to three years or longer. Advances are expected in the therapy as clinical trials conclude. These are likely to see reduced side effects, longer remission periods, lower prices and wider uptake of the radioisotope + ligand.

Some Factors in favour of Radioligand Therapy

The radioactive source is cleared from the body in 7 days.

No overnight hospitalization is required (except in Europe – 24 to 48 hours).

It is safe, painless and convenient with only moderate fatigue being experienced by some men.

It allows multiple cycles of radiation with variable doses also possible.

This therapy is the subject of an enormous research and regulatory effort (clinical trials) which will see the performance of the therapy rapidly advance.

It appears that RLT can be safely used after ADT, chemotherapy or immunotherapy. It is likely that RLT will be co-administered with one or more of these therapy classes in the future.

Some Factors against Radioligand Therapy

RLT is still regarded as an experimental therapy and it will be 2H 2020 at the earliest, before any jurisdiction fully approves the treatment.

It is very expensive with no medical insurance likely to be available.

Some men have no or limited PSMA receptor response to the ^{68}Ga-PSMA-11 tracer and the ^{177}Lu-PSMA-617 therapeutic. Even amongst men who have shown tracer uptake on PET imaging, some found their PSA reduction to be much less than others; that is, less cancer cell killing capability.

Its long-term efficacy is still not yet known.

Side effects include xerostomia (mouth dryness) in 68% of men, grade 1 to 2 nausea in 48%, and grade 1 to 2 fatigue in 36%. Grade 3 to 4 toxicities were infrequent and included thrombocytopenia (low platelet count) and anaemia (low haemoglobin) in 10% of patients.

(Whilst the WCMC dose escalation trial has shown a treatment protocol that avoids xerostomia (mouth dryness), many facilities have not yet adopted this protocol).

Chapter 9.

Hyperthermia

The ancient Greeks treated sick patients with heat. In 500BC, Parminides, a Greek physician was purported to say, ‘Give me a chance to create a fever, and I will cure any disease.’ The Egyptians were said to have treated tumours with heat as early as 5000 BC. There are documented occasions where cancer patients who have been subjected to prolonged high fever due to being stricken with an infectious disease, have seen their cancer regress as a result of being exposed to higher than normal body temperatures.

Hyperthermia (also called thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures. Research has shown that elevated temperatures of between 39° C (102° F) and 48° C (118° F) can damage and kill cancer cells, usually with minimal injury to normal tissues. Hyperthermia treatment, when combined with other treatments such as chemotherapy or radiation, usually leads to a significant reduction in tumour size. Some hyperthermia treatments in themselves lead to good treatment outcomes. Other than for some prostate cancer treatment regimens, hyperthermia is usually non-invasive. There are two broad forms of hyperthermia treatment: whole body hyperthermia and local or regional hyperthermia. Both techniques have been practiced in a number of European clinics for more than 20 years, with patients travelling from all over the world to undergo treatment. It is used for treating several types of cancer such as prostate, breast, throat, tongue, etc.

Whole body hyperthermia (WBH)

This form of treatment sees the whole body (except for the head) being subjected to a higher than normal body temperature. It is often used in patients where metastases have taken hold with secondary cancers appearing in the lymph glands or other organs. Changes take place in body cells when they are exposed to higher-than-normal body temperatures. These higher temperatures see the “elevation” of heat shock proteins from the cancer cells, which allow the body’s own immune system to better see these cancerous cells and attack them. This ‘elevation’ of heat shock proteins, also allows lower doses of chemotherapy or radiation to kill these cancer cells.

In whole body hyperthermia, the heating is accurately controlled and is provided by either microwave or infrared energy. The patient might be treated for one to several hours at a time with two, three or four follow-up treatments being planned over a ten day or longer period. It is usual that the patient also receives an adjuvant treatment such as chemotherapy during, or after the whole-body hyperthermia treatment. This form of treatment usually sees temperatures limited to a maximum of 42° C (108° F). In Europe, the method of heating is almost exclusively via infrared, for a number of reasons:

Infrared units (special LED radiators deliver computer-generated water-filtered IR A-type wavelengths that penetrate the skin to deliver heat to the capillary bed) have been found to preferentially stimulate the immune system, whereas microwave units do not obtain an immune response. They do not develop hot spots or burn the patient as is possible with microwave devices.

Radiation treatment after hyperthermia also yields good outcomes, but chemotherapy appears to yield the best results. Research has shown that WBH can have a significant beneficial effect on the immune function of an organism infected with cancer. The introduction of infrared A-type generated heat, sees the tumour go into apoptosis (cell death). This is achieved by metabolic exhaustion, loss of ATP production, hypoxemia, an increase in lactic acid and the production of heat shock proteins. The surrounding healthy tissue is actually improved by WBH due to better oxidation, higher production of ATP, higher blood flow, and the increase and activation of immune cells.[1]

More generally, WBH is often used as a treatment of last resort. The German clinics offer an integrative approach to treatment and have achieved excellent results. The protocol used at the St Georg Clinic, near Munich, Germany, sees the body heated to 41.6-41.8° C (107° F) for 90 minutes. A temporary state of hyperglycaemia, using glucose, is induced in the patient to improve tumour response. Low-dose chemotherapy and/or natural therapies such as intravenous vitamin C (25-50 grams) are administered. The resultant high acidity and hypoxia damage the blood vessels that feed the cancer cells and WBH damages the membranes, proteins and enzymes of the cancer cells, thus leaving them more vulnerable to attack by the anticancer agents that have been introduced.

WBH is still considered as an experimental treatment in many countries, including the USA. Converse to this, is the fact that the treatment is covered by health insurance policies in Germany. The latest machines are considered to be very effective in treating mCRPC patients.

Local and Regional Hyperthermia

Local or regional hyperthermia is the use of heat applied directly to an area of the body, usually the cancer tumour. This kind of hyperthermia has been used alone or in combination with such therapies as chemotherapy and radiation, to treat a wide variety of cancers including prostate cancer, with excellent results. These cancers include melanomas, oesophageal or stomach cancers, pancreatic cancers, sarcomas, bone tumours, cervical cancers, head and neck cancers, and rectal cancers. Hyperthermia causes direct cytotoxicity in the tumour, enhances its sensitivity to radiation, and improves the effectiveness of many chemotherapeutic agents in sometimes drug-resistant cells.[2]

The heat is generated by radio frequency, microwave, ultrasound, or magnetic energy. The heat is applied to the body surface, inside body cavities or into deep body tissue via the use of needles or probes. Local hyperthermia is used to treat a small body area or a small organ which contains one or more tumours, such as prostate cancer. When it is used to heat a larger part of the body, such as an entire limb or larger organs, it is referred to as regional hyperthermia.

In 2011, the US Food and Drug Administration approved the first RF device (the BSD 2000 from the BSD Medical Corporation, Salt Lake City, Utah, USA) for the treatment of cervical cancer to be followed by radiation treatment. BSD Medical Corporation is now called Pyrexar Medical and have an updated product offering. Their BSD-2000/3D provides targeted deep regional therapeutic hyperthermia to solid tumours by applying radiofrequency (RF) energy. The BSD-2000/3D delivers energy to a patient using a power source and an array of multiple antennae that surround the patient’s body.

Hyperthermia is now being used alongside high dose brachytherapy and now with other radiation and chemotherapy modalities. The Maryland Proton Treatment Centre has become the first centre in the world to bring the benefits of deep-tissue hyperthermia to high-precision proton therapy. The Baltimore-based facility plans to administer hyperthermia in combination with proton therapy after evaluating supporting evidence and studies that suggest the addition of heat sensitizes tumours to radiotherapy and chemotherapy, allowing both to significantly reduce the size of tumours.

“Protons minimize the radiation spill over to critical structures and healthy tissue. If you combine with heat, you can really get more out of this limited dose of radiation that you are trying to deliver a second time," said Zeljko Vujaskovic, a professor of radiation oncology at the University of Maryland School of Medicine, when referring to salvage therapy.

Oncotherm GmbH is a European company that has over 450 of their Oncotherm units in clinics around the world. They claim their units are treating more than 200,000 patients a year, with most not being for prostate cancer. However, their Oncotherm EHY-1020 is specifically designed to treat prostate diseases, with both malignant and benign tumours (BPH) being treated. It uses a catheter with built-in electronics and counter electrode. It claims to drop the patient's PSA by up to 25 times over a six-month period. The method has been used successfully since 2010 with good success rates and minimal side effects. Its therapeutic success was confirmed in a 123-patient study that reported that over 95% of men had a successful outcome, whilst maintaining a high quality of life. In some cases, the patient had a need for re-treatment after 3 years.

An Australian, and similar clinics in Austria, Belgium, Canada, China, Denmark, Germany, Greece, Hungary, Israel, Italy, Jordan, Romania, Russia, South Korea, The Netherlands, Turkey and Ukraine offer cancer treatment using at least one of the Oncotherm systems. The first oncothermia clinic in Australia opened at the Prince of Wales Hospital in 2012.

Local hyperthermia usually targets a small area such as the tumour itself. The tumour is accessed directly via needles or probes and is referred to as interstitial hyperthermia. The low blood flow in cancerous cells, contributes to their rapid temperature increase under hyperthermia conditions, whereas the healthy cells adjacent to the tumour have normal blood flow that rapidly dissipates the heat build-up. Thus, a temperature gradient is created between the cancer cells and the normal cells. The tumour mass becomes inactive at 42° C (108° F) or higher temperatures. The temperature of the healthy cells is limited to a maximum of about 40° C (104° F), by the cooling effects of normal blood flow. They are not adversely affected by the induced heat.

The heating of the cancer cells also leads to the release of heat shock proteins (HSPs) by the cancer cells. HSPs are found in almost all living organisms, from bacteria to humans and when subjected to heat shock as they are in hyperthermia, their expression is increased (or in illustrative terms, they put up a flag which says "here I am, come and get me"). This action 'allows' the cancer cells to be identified by the body’s immune system and makes them far more vulnerable to attack by one’s own immune system, radiation and by low dose chemical or biological agents. Therefore, hyperthermia is usually used in conjunction with one of these main stream therapies.

Local hyperthermia kills cancer cells by:

Tissue acidosis (as cells become more acidic, they become more heat-sensitive).

Damage to poorly developed blood capillaries.

Damage to tumour cell membranes, proteins and enzymes.

Cellular repair mechanism failure.

DNA and RNA synthesis changes.

Failure of antioxidant systems.

Impact on heat shock proteins (HSP), which are made more ‘visible’ to the body’s immune mechanisms.

A number of different modalities exist for localized hyperthermia. These include:

thermo-radiotherapy; microwave hyperthermia; transrectal ultrasound; radio-frequency interstitial tumour ablation; transrectal hyperthermia; thermo-immunotherapy and transurethral hyperthermia (TUH). These were reviewed in a paper by Douwes and Lieberman, published in the June 2002 issue of Alternative & Complementary Therapies.[3] This latter paper focussed in the main on transurethral hyperthermia (TUH) which is a speciality of Dr Douwes's Clinic St. Georg in Germany. They have successfully treated many hundreds of early stage prostate cancer sufferers over more than 20 years. They also treat advanced prostate cancer cases using whole body hyperthermia with adjuvant chemotherapy or conformal radiation treatment.

TUH treatment introduces the RF generated heat, via a thin probe inserted into the prostate via the urethra and penis. This probe also includes a temperature sensor that is used to very precisely control the procedure. The Douwes TUH protocol sees the prostate temperature raised to 47 - 49° C (117 - 120° F) and maintained in this range for up to 60 minutes. Research has shown that the optimum 'killing' temperature is at or above 43° C (109° F) and that time duration and temperature optimize hyperthermia treatment.[4],[5],[6] Two or three treatments over a week appear to be their norm. Generally, they also treat patients with large doses of vitamin C and other complementary anti-cancer agents during the outpatient visits to the clinic. The medical professionalism and proficiency in hyperthermia-centred cancer treatment of the three or four German clinics offering hyperthermia treatment is well-established and they treat large numbers of patients from all over the world.

One issue that might be of concern to prostate cancer sufferers is the absence of clinics outside of Germany and Austria that use TUH therapy. I asked a manufacturer of a temperature-based prostate cancer therapy as to why there were not TUH clinics everywhere. His response was that local hyperthermia had one drawback. This was that cancer cells immediately adjacent to normal blood pathways were able to dissipate the induced heat before cell apoptosis took place. A likely response from the clinics using TUH would be that the temperature elevation and its duration are sufficient to achieve cell apoptosis. It also ensures that the heat shock proteins are activated making the cancer cells susceptible to attack by the body's own immune system and the chemical and biological agents introduced during the TUH treatment.

My brother, who had Stage 4 prostate cancer, was treated with local hyperthermia and intravenous Vitamin C at an integrative health clinic in Melbourne in 2015. Due to the condition of his kidneys, the clinic was unable to optimize their dosages, resulting in a less than optimum outcome.

Summary – Hyperthermia

Hyperthermia is a type of cancer treatment in which body tissue is exposed to temperatures of between 39° C (102° F) and 48° C (118° F) for sustained periods. This practice damages and kills cancer cells, usually with minimal injury to normal tissues.

At these temperatures, heat shock proteins become more “visible” to the body’s immune system and the cancer cells are more vulnerable to attack by low dose chemotherapy or other biological agents.

The Douwes local transurethral hyperthermia (TUH) protocol sees the prostate temperature raised to between 47 and 49° C (117 - 120° F) and maintained in this range for up to 60 minutes. The heating is radio-frequency induced and is precisely monitored and controlled. For TUH, the optimum ‘killing’ temperature is considered to be at or above 43° C (109° F) with both time duration and temperature considered important.

Best results are obtained when the TUH protocol is used in conjunction with a complete androgen blockage (treatment with gonadotropin-releasing hormone). Whole body hyperthermia is used in many countries to treat metastatic cancers.

Some Factors in favour of TUH

It is a simple, low cost procedure.

It causes direct cytotoxicity (cell death) in cancer cells and makes them additionally susceptible to chemotherapeutic and biological agents.

Some Factors against TUH

Radio-frequency local TUH is only available from clinics in Germany and Austria.

Small possibility of the survival of some cancer cells that are immediately adjacent to normal blood supply vessels. (The desired ‘killing’ temperature is not achieved for the required duration due to the heat removal by the blood supply). The simultaneous use of biological and chemotherapeutical agents is used together with the enhanced immune system of the body, to destroy these remaining cancer cells.

The US FDA has approved microwave-induced hyperthermia only when it is used in conjunction with radiation treatment.

Chapter 10.

Cryotherapy

Cryotherapy is also known as cryosurgery or cryoablation. It is a procedure in which cancer cells are killed by freezing them by surrounding them with ice crystals. Tiny needles are inserted into the prostate under TRUS (transrectal ultrasound) guidance. Argon and helium gases are introduced sequentially via these needles into the cancerous zones of the prostate which provide a cooling and subsequent heating cycle. The urethra, which goes through the penis and through the centre of the prostate, is protected by a heated catheter to protect it against freezing and resultant damage. The American Urological Association recently issued Best Practice Guidelines for the use of cryosurgery for the treatment of prostate cancer.[1] It provides considerable information on cryosurgery and I consider it essential reading for anyone contemplating cryotherapy, either as an initial treatment or as a salvage treatment after biochemical recurrence of the disease. Refer to the Appendix 3 for their web site details.

Primary prostate cryoablation is also recognized by the EAU as a treatment for prostate cancer. A detailed patient selection criteria guideline is available from their web site.

AUA’s recommended guidelines on primary prostate cryoablation include:

Clinically organ-confined disease of any grade with a negative metastatic evaluation.

A PSA level of ≤10.

Gleason score 7 to <8 with a PSA level >10 to <20 ng/mL and/or clinical stage T2b.

Patients with a prior history of transurethral resection of the prostate (TURP) are not recommended for primary prostate cryoablation.

Cryotherapy is generally used in patients with low-risk tumours. PSA levels less than 10 ng/ml, Gleason score lower than 7, and Stage T1c or T2a, and some say, even up to T3a. The risk of temporary or permanent impotence after the procedure is significant which considerably reduces the number of men undergoing cryotherapy. It is also an alternative procedure for patients who have had cancer return after radiation therapy.[2] It has a part to play in cases where the cancer has spread just beyond the prostate. Cryotherapy is unlikely to be recommended for men who have a very large prostate due to the difficulty in freezing larger areas whilst containing the freezing to tissue adjacent to the prostate.

This form of prostate treatment started in the 60’s, but went into decline due to relatively poor outcomes being achieved. At that time liquid nitrogen was used as the coolant. The technique re-surfaced again in 1993, after significant improvements in the available equipment, a change to argon and helium gases and TRUS guidance becoming possible. Due to the selectivity of patients suited to cryotherapy and the relatively small number of patients undergoing the technique, few long-term studies appear to have been done to prove its efficacy, etc. One study by D. Bahn, et al., published in 2002, reported on the seven-year outcomes of 593 patients treated with cryoablation as the primary prostate cancer treatment. The study concluded that no serious complications were observed and that: “cryoablation was shown to equal or surpass the outcome data of external-beam radiation, 3-dimensional conformal radiation, and brachytherapy. The 7-year outcome data provide compelling validation of TCAP (the cryoablation of the prostate) as an efficacious treatment modality for locally confined and locally advanced prostatic carcinoma.” However, the study revealed almost 95% of men who were potent before the treatment, were impotent after cryoablation. The remaining 5% regained their erectile function an average of 16.4 months after treatment. For those with normal urinary control before the procedure, the incontinence rate was 84% post treatment, with an average 6.1 months post treatment recovery time.[3] Since this study was concluded, there have been considerable improvements in the thermal equipment used and the capability via advanced imaging techniques to more accurately ‘see’ the areas to be ablated. Today, some urologists may have patient specific reasons for recommending this technique which from more recent studies undertaken, suggest it is a safe and effective treatment.

Serious risks are:

Erectile dysfunction (impotence) for > 80% of men, which is usually permanent, dependant on the extent of the ablation and the technique used.

Urinary incontinence is rare; (except in cases of cancer recovery treatment after prior radiation therapy).

Fistula (an abnormal opening) between the rectum and bladder is a rare complication with newer systems.

Generally temporary conditions are:

Bleeding or blood in the urine.

Swelling/soreness in the area where the needles are placed.

Swelling around the penis or scrotum.

Pain and burning sensations in the bladder/intestinal region.

Urge to empty the bladder and bowels more often (most men recover normal function in several weeks).

The urologist usually provides a pre-procedure information sheet that advises the patient what to do before the procedure as regards existing medication being taken, bowel emptying regime, etc.

Today, the procedure is generally done as an outpatient procedure (or 24-hour hospital stay) under regional (epidural) or general anaesthetic. A catheter is placed via the penis into the bladder and the bladder filled with a saline solution. A warm liquid will be passed through this catheter during the freezing stage of the procedure to ensure the urethra is protected from the freezing. The urologist will insert the needles (often called cryoprobes) and temperature sensors through the perineum area between the anus and the scrotum via a template insertion grid. Their positioning is usually assisted by a TRUS-generated ultrasound image. Liquid argon is then passed into the needles which see the cancerous prostate tumour quickly frozen. The temperature probes monitor the temperature of the neurovascular bundles, the apex, the Denonvilliers' fascia area and external sphincter. The tissue being treated is held in this frozen state for a few minutes, before it is thawed by the introduction of helium through the needle probes.

On occasion, the urologist may decide to repeat this cycle. This is done more often than not when the treatment is a salvage procedure by ablating the posterior area of the prostate during the first freezing cycle followed by the anterior area during a second cycle. The needles are withdrawn, but the catheter is left in place for one to two weeks whilst the prostate gland heals and all swelling disappears. Impotence (erectile dysfunction) will occur in most men who have this treatment due to nerve damage caused by the freezing process.

The SeedNet Gold™ cryotherapy system is a recent innovation from Galil Medical Inc. It offers urologists a comprehensive minimally invasive solution to treat prostate and renal cancers. SeedNet Gold™ has apparently gained wide acceptance by urologists due to its ease of use and controllability. The former Director of the Prostate Cancer Institute, St George Hospital, Sydney, Australia, in 2013 said:

“The Prostate Cancer Institute will be the first centre in Australia to introduce regular cryotherapy treatment for prostate cancer, which makes us the only public institution in Australia capable of providing all treatment options for prostate cancer.” (Author’s note: Proton Beam Therapy is not yet available in Australia).

“Today, minimally invasive treatments are in demand. When used in combination with extremely low/sub-zero temperatures and image monitoring, the cryotherapy system is a safe, effective and minimally invasive treatment for prostate cancer,” he concluded.[4]

Galil Medical recently added the SeedNet Gold™MRI cryotherapy system and the Visual-ICE® Cryoablation System to their existing product range. The former unit is claimed to be the only cryoablation system on the market that is compatible with MRI scanners, providing clinicians with an option to treat tumours under MRI guidance. The latter is claimed to be the most technologically advanced system in the marketplace.

In a report where men had a half prostate ablation using cryotherapy in 55 men with at least one-year follow-up, 95% had stable PSAs and 86% remained potent, despite 29 of the men being of medium or high risk of a recurrence. Seven men had to be retreated due to cancer developing in the other half of the prostate that was not subject to ablation. Of the 54 men without previous surgery or radiation treatment, all were continent. The authors of this research, G.Onik, et al, concluded that: “their preliminary results showed that a ‘male lumpectomy’ – in which the cancer region itself was destroyed – preserved potency in most patients and limits other complications (particularly incontinence) whilst maintaining good cancer control.”[5] You will have noticed that there is a huge variance in incontinence and impotence levels reported between the Bahn study (reported on earlier in this chapter) and the Onik study. The latter study focussed on the cryoablation of a specific tumour, with large areas of the prostate being unaffected, thus maintaining their function. The high potency rate (84%) and 100% continence level achieved, suggests there was no damage to the neurovascular bundles in most cases. Certainly, the future of cryotherapy is in using the latest technology that allows only part of the prostate (tumour only) to be ablated, with a strong likelihood of potency and continence being retained. A recently improved FDA-approved urethral warming device has minimized urethral complications. However, all cryoablation patients need urethral catheterisation for 5 to 15 days or in rare cases for even longer, after undergoing cryotherapy.

Focal cryotherapy with its smaller needles and advanced temperature control will undoubtedly benefit from the non-invasive qualities of mpMRI and Colour Doppler ultrasound to confirm the size, shape, location and density of solid adenocarcinomas in the prostate. Better spacing of the probes now contributes to the effectiveness and safety of the procedure.

Summary – Cryotherapy

Cryotherapy for prostate cancer, until recent years, presented patients with almost certain impotence.

Recent technological advances have allowed the technique to find more widespread use as a focussed procedure where individual tumours are ablated with minimal damage to surrounding tissue.

It is used as a salvage technique for many radiation patients who have had a recurrence of their cancer.

Some Factors in Favour of Cryotherapy

It is suitable for patients regardless of their Gleason score.

It is a minimally invasive outpatient procedure that yields good outcomes in the hands of a surgeon well experienced in the technique.

It can provide an adequate margin around the tumour and can treat areas immediately external of the prostate.

If there is a recurrence of the cancer, the procedure can be repeated with radiation therapy, chemotherapy or a prostatectomy being options.

It is suitable for many men who have prostate cancer that is resistant to radiation, hormone therapy or chemotherapy.

It is generally one of the lowest cost interventional treatments for prostate cancer.

Some Factors against Cryotherapy

It requires extensive experience and training by the surgeon. Make sure your surgeon has done many such procedures and that the procedure is not done as a ‘training’ exercise.

It generally requires use of catheterisation for some days due to the swelling of the prostate.

Long term studies using the more recent equipment have not been concluded to date.

Chapter 11.

High Intensity Focussed Ultrasound

High Intensity Focussed Ultrasound is usually referred to as HIFU. This technique has been around since the late 1990’s with two competing brands dominating the market: the Sonablate 500®from SonaCare Medical LLC, USA and the Ablatherm® Robotic HIFU and Focal One® from EDAP TMS S.A., Lyon, France. The latter is widely used in Europe and has subsidiaries in Italy, Germany, USA, Japan, Korea and Malaysia. The Sonablate 500® is used mainly in Japan, the USA, Australia and other countries. In October 2015, SonaCare Medical announced that it had received FDA approval to market the Sonablate® 450 in the U.S. for the ablation of prostate cancer lesions. SonaCare Medical can now offer a full HIFU surgical suite of technologies working off of the same basic platform which will provide benefits throughout health care centres.

To date, more than 70 US urologists have treated 1800 patients using the Sonablate® 450 since it was approved for use in the USA. The three-fold dogma of ‘surgery, radiation and chemo’ has become a four-fold dogma of ‘surgery, radiation, ablation and chemo.’

Now that the two brands have achieved 510(k) approvals in the USA, the many American patients having HIFU treatment in Bermuda, Nassau, or Canada will decrease as more and more HIFU systems are installed in the USA.[9]

The technique involves heating the prostate via an ultrasonic probe placed in the rectum. At the point of focus, the tissue heats up to 70° to 90° C (158° to 194° F) and this results in the tissue dying of coagulation necrosis - (blood clotting and localised death of living cells). It is completed in a couple of hours and outcomes are generally excellent.

The robotic HIFU probe is inserted into the rectum under anaesthesia. A crystal within the probe vibrates at a specific frequency when an electrical current passes through it, and this produces ultrasound waves. The ultrasound waves pass through body tissue and some of the waves are reflected back to the crystal that produce an image of the prostate and its surrounding structures on a screen, which can be viewed by the urologist. By increasing the intensity of the ultrasound waves and focusing the waves on a single point (like a magnifying lens), high energy is delivered to the prostate tissue, releasing heat that causes permanent tissue ablation (cell death) of the prostate cancer. Dead tissue is passed out of the prostate with urine.

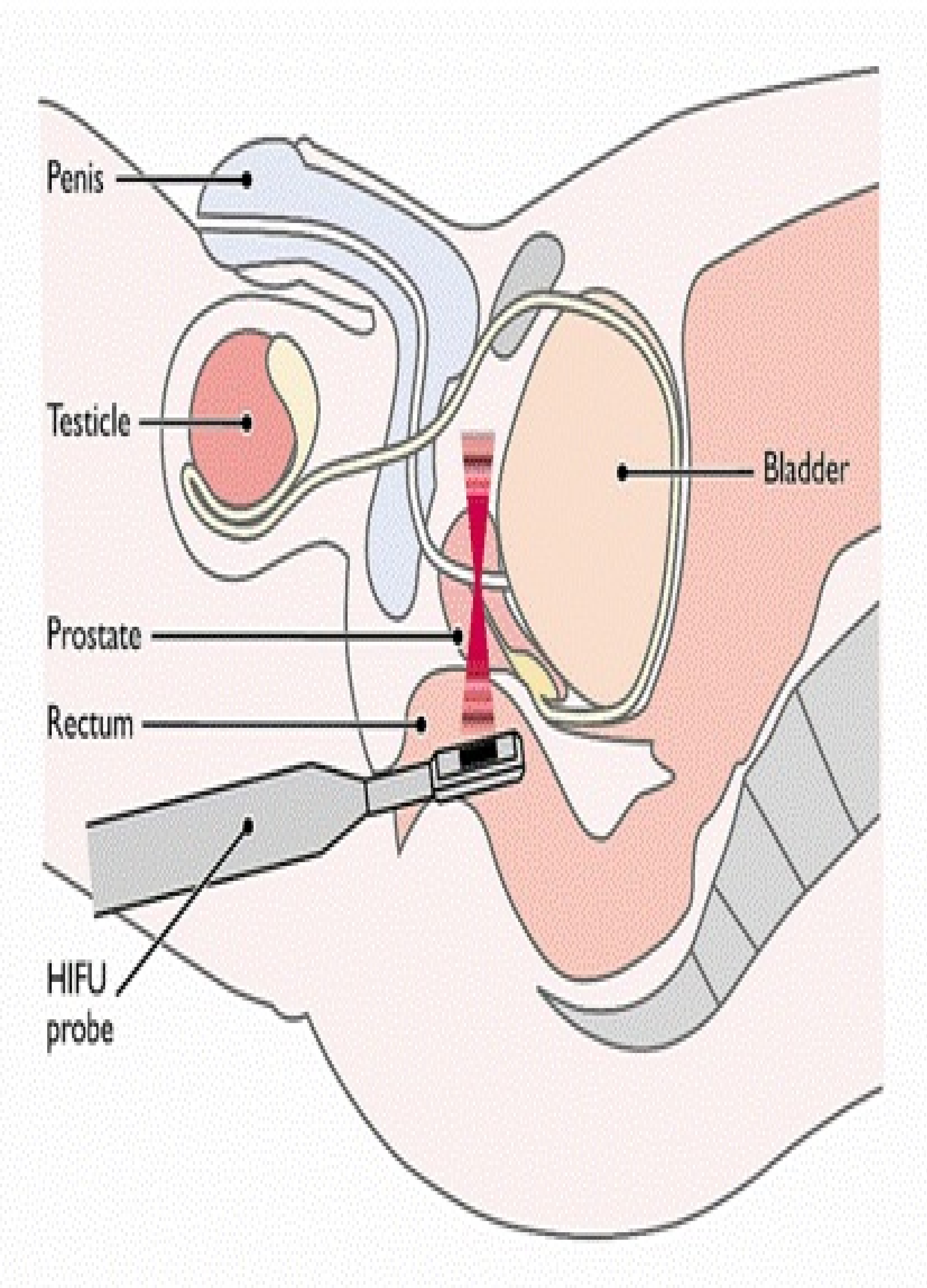

Penis
Testicle
Bladder
Prostate
Rectum
HIFU probe

Image: Courtesy of Orchid Cancer, St Bartholomew’s Hospital, London

HIFU presents very manageable short-term complications with possible long-term complications being urethral stricture risk (9%), which may require urethral dilation or incision, stress incontinence (4%), urinary incontinence (12%) and erectile dysfunction. The International Index Erectile Function (IIEF) showed overall sexual activity reduced by 20%, and specific erectile function reduced by 25% at 6-12 months after HIFU. The risks of HIFU compare favourably with Robotic Radical Prostatectomy and are generally comparable to Brachytherapy/Radiation Therapy. Perhaps a more important measure is the recurrence rate of prostate cancer across the spectrum of available treatments. There is no standardised definition of what is a biochemical recurrence or failure that covers the various treatment types available. The Prostate Cancer Research Institute in the USA, in their PCRI Insights publication (March 2011, Vol. 14: No 1) attempt to ‘standardise’ a definition and include a table of comparable disease free periods reported in key scientific studies covering the four common treatments: (HIFU; HDR brachytherapy + IMRT; Cryotherapy; Prostatectomy).[1],[2],[3]

In many instances, low or intermediate risk prostate cancer patients, have their prostate cancer confined to one lobe (or part of one lobe) of the prostate. In these instances, focal HIFU treats only the side or area of prostate proven to have cancer. This is referred to as hemi-ablation or TFT (Targeted Focal Therapy). Destroying part of the prostate to treat prostate cancer may be just as effective as removing the entire organ, but without many of the distressing side-effects that tend to accompany the more invasive operation, according to UK investigators. A study using HIFU hemi-ablation at University College London has demonstrated feasibility, safety and encouraging functional outcomes (95% preservation of urinary/sexual function) and encouraging early cancer control (90% absence of any prostate cancer on protocol mandated biopsies).[5]

SonaCare Medical recently reported the results from a multi-centre study following Sonablate HIFU treatment of 625 medium- to high-risk clinically significant non-metastatic prostate cancer patients. With a median five-year follow-up, failure free survival at one, three, and five years was 99%, 92%, and 88% respectively, equivalent to that achieved with surgery. Metastasis-free, cancer-specific, and overall survival at five years was 98%, 100%, and 99% respectively. The study additionally reports that 98% of men, maintained pad-free urinary continence after their procedure and 85% maintained erectile function, both material improvements over that seen with surgery and radiation therapy. The HIFU side effect profile was far better as regards to the patient’s quality of life post-procedure than was surgery. (A recent report from the U.K. on 1,000 patients who underwent a radical prostatectomy found maintenance of pad-free continence at only 65% versus 2% for HIFU).

"Focal HIFU is a major shift in treating men with early prostate cancer. Our study shows that cancer control in the medium term is very good and importantly, men can expect a low-risk of side effects such as incontinence and erection problems,” states Prof. Hashim Ahmed, Chair of Urology, at Imperial College London and contributing author to this study. “All men who are suitable for focal HIFU should be told about this treatment option so they might consider it as an alternative to radical prostatectomy or radiotherapy."

“This is a landmark study in the treatment of medium to high-risk prostate cancer authored by one of the leading clinical research groups in the field,” adds Dr. Mark Carol, CEO of SonaCare Medical. “This study shows it is possible to achieve whole-gland equivalent cancer control rates without the concomitant side effect profile of whole gland treatments. Now, otherwise healthy men with prostate cancer can leave the hospital post focal HIFU treatment with their cancer under control yet still healthy. They can even return back to work and activities of daily living the very next day instead of having to wait the weeks required with surgery. This represents a remarkable achievement and a treatment option that should be made available to all men with prostate cancer.”

HIFU has been widely used in Europe for more than 20 years, particularly for whole prostate ablation of the elderly, who may not have been able to cope well with EBRT or radical prostatectomy. A study by the Belgium KRE published in 2009, reported that an estimated 730 men were treated with HIFU in four Belgium hospitals between 2000 and 2008. A number of these patients had HIFU as a salvage treatment after a recurrence of the disease. Again, this study reported the absence of randomised controlled studies and called for such studies before any possible endorsement of HIFU.[7]

HIFU and Multiparametric MRI

Multiparametric MRI is becoming an increasingly popular tool in the diagnosis of adenocarcinoma tumours of the prostate. Software has now been available for at least six years that ‘merge’ or ‘fuse’ the imaging capability of MRI with ultrasound images. This allows real time visualization of tumours not usually seen by ultrasound. This capability offers the potential for tumours to be ablated by HIFU (or FLA) in real time under MRI imaging and control. This technology provides the capability to ‘destroy’ the tumour alone whilst sparing healthy adjacent tissue. (See TULSA below).

With improvements in MRI technology and software, MRI guided biopsies (MRGB) are being done without the need to fuse the doppler ultrasound image with the MRI image to map the lesion/s, prior to HIFU, FLA or similar intervention. The patient characteristics of men suited to focal therapy are:

The prostate should have a discrete lesion on MRI that should have definable margins.

The MRI-identified lesion needs to be associated with clinically significant cancer.

The lesion is treatable and a margin can be applied to it.

The rest of the prostate needs to be significantly cancer free on MRI.

The patient should place a high level of importance on maintaining normal sexual and urinary function.

SonaCare Medical's Sonafuse, their HIFU fusion platform, uses an open architecture approach to integrating Sonablate planning software with existing mpMRI fusion biopsy platforms in the market. Segmented and annotated DICOM radiology images are imported into Sonablate from the physician's preferred fusion solution and fused with live ultrasound images to enable targeted HIFU planning.

EDAP TMS, the manufacturers of the Ablatherm® system, have introduced their newest HIFU product offering, this being the Focal One® Robot-Assisted Prostate Tumourectomy System. The Focal One was successfully used for its first prostate tumour removal in both France and Germany, some years ago. By combining all the latest technologies in imaging and treatment, the newest Focal One provides a state-of-the-art focal system with MR-fused imaging, a non-invasive surgical approach, precise and efficient therapeutic energy and end-of-treatment validation imaging capability.

EDAP TMS announced in November 2015, that it had received 510(k) clearance from the FDA to market their Ablatherm® Integrated Imaging HIFU in the USA for the ablation of prostate tissue. The FDA approvals of the two rival integrated devices, will see a very rapid take up of this technology in the USA.

One of the other focal therapies, Focus Laser Ablation, is considered in the next chapter. As HIFU and FLA are very similar techniques, many of the comments for FLA apply equally to HIFU. HIFU gets significant coverage in the European Urology Association’s Guidelines on Prostate Cancer Updated April 2014 (See reference in next chapter). These guidelines include a section on complications suffered by HIFU patients.

The new imaging capabilities of mpMRI have been significantly enhanced by the use of image registration software (also called fusion software). It uses a complex set of computer algorithms to overlay and digitally marry two different imaging processes such as ultrasound and MRI for more complete visual information. This can be done in real time in the urologist’s rooms (with a previously-captured MRI image) whilst a patient is undergoing a TRUS procedure. Most proprietary or customised software has the capability of “elastically” adjusting the MRI image from point to point to get an exact match between the two image sources. This capability is called deformable or non-rigid registration and allows the combined images to be rotated in any plane. HIFU, when used with mpMRI, is likely to come into the main stream of prostate cancer therapy in coming years.

The technique has already moved out of the research arena into daily use at hospitals like the Royal Marsden Hospital in London. The increased precision in focussing the HIFU beam allows even small tumours to be heated to 55° C (131° F) for one minute which is sufficient to kill all cancer cells in the tumour. Healthy cells are unaffected by this level of heating.

MRI-guided transurethral ultrasound ablation -TULSA

An ablative technology for the removal of malignant prostate cancer tissue was recently introduced by Profound Medical Inc, Toronto, Canada. Their TULSA-

PRO® system is a novel technology which combines real-time MRI, robotically-driven transurethral ultrasound and closed-loop thermal feedback control to remove malignant prostate cancer tissue. The MRI-guided system is CE marked in Europe and has investigational status in the USA as part of the TACT pivotal trial.

In the TACT Phase 2 study at 13 institutions in five countries, nearly all of the 115 men (96%) met the primary end-point of PSA reduction ≥75% and yielded a post-treatment median PSA of 0.34 ng/mL. In men with a Gleason score of 3+4 or higher, 79% were free of cancer a year later. With better patient recruitment, this percentage might have been much higher.

The system is designed to provide customizable and predictable ablation of a surgeon-defined region of the prostate while actively protecting the urethra and rectum to help preserve the patient’s natural functional abilities. TULSA is different from HIFU, employing a peripheral stream of ultrasound with a continuous sweeping rotation. HIFU's ultrasound comes through the rectum to the prostate; both technologies ablate a selected portion of the prostate.

The TULSA procedure takes place in a MRI suite, under general anaesthesia, with a team that includes a urologist and radiologist. The tumour/s and prostate are mapped via a trans-urethral probe. The patient also has a subrapubic tube that goes through the abdomen into the bladder and stays in place for about 2 weeks after the treatment. Median treatment delivery time is 51 minutes, which offers cost advantages to patients, compared to HIFU or RPP patients.

The TACT study found that at one year, 20% of patients had grade 2 erectile dysfunction, median change in International Index of Erectile Function (IIEF-5) was -3 (-13 to 0,), and 69 (75%) of 92 men maintained erections sufficient for penetration (IIEF Q2 ≥ 2).

Alan Priester, PhD and urological researcher at University of California, commented that the reported impotence rates were below par. "While this is better than radical prostatectomy, it is worse than reported values for most focal treatments such as focal HIFU or hemi-gland cryo-ablation," he said. Of 112 men with 1-year continence data, 1% were incontinent (more than 1 pad/day), daily leakage increased 4%, and 8% wore a pad.

Yet again, every prostate cancer sufferer has a price to pay for their treatment, regardless of the therapy used.

Summary – HIFU

HIFU involves heating the prostate via an ultrasonic probe placed in the rectum. At the point of focus, the tissue heats up to 70° to 90° C (158° to 194° F) which results in tissue death.

The risks of HIFU compare favourably with Robotic/Radical Prostatectomy and are generally comparable to Brachytherapy/Radiation Therapy.

HIFU is equally successful in ablating the whole prostate (almost always in the very elderly); one lobe (half) of the prostate or a targeted tumour (or in a multi-tumour situation).

Fusion software is now widely in use that merges a mpMRI image with the ultrasound image. This capability offers the potential for tumours to be ablated by HIFU (TULSA or FLA) in real time under MRI imaging and control. This is a ‘game-changing’ scenario which when combined with the newest HIFU systems from the two dominant manufacturers (and now the TULSA system), is set to significantly increase the number of patients undergoing HIFU as a primary treatment. It also has a place in salvage treatment.

Some Factors in favour of HIFU

It is generally an outpatient procedure that allows the patient to go home after recovering from the up to three-hour treatment and recovery from the anaesthetic.

It is repeatable and can be used as a primary or salvage treatment.

It does not preclude other treatments if HIFU fails.

The increase in imaging provided by mpMRI alone or when combined with a Doppler ultrasound image, allows precise ablation of individual tumours.

Some Factors against HIFU

Whilst a few randomised controlled studies exist as yet the longer-term outcomes using mpMRI-guided HIFU ablation are under-reported.

The procedure is costly in some jurisdictions with sometimes limited re-imbursement from health funds.

It is typically only used in cases with a Gleason score of 7 or less.

Chapter 12.

Focal Laser Ablation

Recent advances in multiparametric MRI (mpMRI) imaging have revolutionized the treatment of prostate cancer. More and more hospitals are upgrading their MRI facilities to incorporate a 3 Tesla mpMRI capability. In Sydney, Australia, most public and private hospitals out of more than thirty now have this capability and more will join them over the next few years. Almost all imaging centres have the latest imaging equipment. Areas of the prostate that appear very suspicious for cancer on mpMRI, have provided extremely high correlation rates for cancer with targeted biopsies.[1] Most clinics and hospitals now rarely perform a random prostate biopsy without first obtaining an mpMRI.

A new treatment, Focal Laser Ablation (FLA), has come into its own as a serious treatment for prostate cancer, due mainly to the impact of mpMRI. FLA is sometimes referred to as LITT (laser interstitial thermo-therapy) and has also been given the name BlueLaser.

With precise mpMRI guidance it is possible to destroy small, early stage tumours using FLA. It should be noted that mpMRI really requires a 3 Tesla strength system, which provides the ability to detect even very small tumours. The earlier 1.5 T machines, even with an endorectal coil, are generally not powerful enough to get the job done properly.[2] A 38-person sample study by David Yao, et al., reported a 6-fold increase in tumours detected by MRI-prompted biopsies compared to conventional non-focused biopsy methods. The anterior lobe and central zone, which are areas characteristically under sampled by conventional biopsies, contained a majority of these tumours. Of the tumours detected via MRI, 93% were clinically significant (≥Gleason 7 or >50% of cores were positive for cancer).[3]

Over the past several years, Dr Dan Sperling, Medical Director and Chief of Interventional Uroradiology at the Sperling Prostate Cancer Centre in New York City, has pioneered a technique for transrectal focal ablation of prostate cancer under MRI guidance. His description of the procedure can be followed at https://www.youtube.com/watch?v=lX1d--Dx56A.

It broadly involves the following steps:

The prostate area is locally anaesthetized.

The prostate is scanned using MRI to identify the size and exact location of the tumour.

A biopsy of the tumour is taken to confirm the diagnosis. Placement of the needle is assisted by visibility on MRI.

A thin laser probe (1.6mm) is introduced into the tumour again under MRI guidance.

The laser ablation is commenced with the tumour heated to destruction within 3 minutes under carefully controlled conditions and MRI imaging.

The whole procedure, which is completely painless to the patient, is completed in about an hour, with the patient going home immediately after being de-briefed by the doctor. The protocol also calls for real time monitoring of the temperature of critical structures adjacent to the prostate (rectum, urinary sphincter and erectile nerves) to prevent collateral damage to the same. Numerous safeguards are built into the system to protect the patient during the ablation process. Dr Sperling has to date treated many hundreds of patients in his clinics in New York and Florida and has reported no significant side effects being experienced by any treated patient.[4] Uptake of the FLA procedure in US medical centres has been reasonably slow, but increasing. This slow take-up rate is probably because laser ablation is only FDA-approved for soft tissue ablation, but has never been officially studied for treating prostate cancer, and is not covered by Medicare or by any major insurance carriers. It became available some years ago in Sydney, Australia on a user pays basis, via a medical practice associated with the Macquarie University Hospital.

Two well-respected clinical institutions, the National Cancer Institute (NCI), and the University of Chicago Medicine (UCM), started clinical trials on Focal Laser Ablation (FLA) in 2013. They were considered as interventional trials, meaning that the treatment was under investigation. The UCM Phase 1 trial reported in the June 2013 Radiology that:

“Transperineal MR imaging-guided focal laser ablation appears to be a feasible and safe focal therapy option for clinically low-risk prostate cancer.” [5]

The results of the MP26-10 Magnetic Resonance Image-guided Laser Focal Therapy for Prostate Cancer: Follow up Results from a Phase 1 Trial appeared in the Journal of Urology in April 2018. 15 patients were included. Median age, PSA, IPSS and SHIM were 66 years, 6.19 ng/ml, 6 and 20, respectively. Median follow-up time was 40.5 months. Nine patients had Gleason 3+4 and 6 had Gleason 3+3 cancer. All patients tolerated the procedure well. Four patients had grade 2 complications (n=2 urinary tract infection, n=1 worsening lower urinary tract symptoms, n=1 bilateral epididymitis). Eight patients had grade 1 complications (n=5 gross hematuria, n=3 minor grade 1 complaints e.g. urgency, small pressure ulcer, post-operative fever). All events resolved completely. Follow-up-targeted biopsies revealed no evidence of cancer in n=10 patients, whereas in 5 patients the follow-up biopsy was positive (n=3 had 2nd FLA session, n=2 underwent prostatectomy). Median PSA at last follow-up (4.79 ±3.32) was significantly lower than prior to treatment (6.19 ±3.76). There was no significant difference between the pre- and post-treatment IPSS and SHIM scores. Patients were followed up at 3, 6, 9, 12, 18, 24 and 36 months with clinical evaluation, PSA, IPSS and SHIM scores.

The trial concluded that mpMRI guided FLA is safe and feasible without any significant change in urinary and sexual function with reasonable oncologic results.

A follow-up Phase 2 Study to Evaluate MRI Image-guided Laser Focal Therapy for Prostate Cancer, a 5-year Survival Study is presently recruiting The primary purpose of this study is to evaluate the feasibility and safety of MRI-guided focal laser ablation (Laser-Induced Interstitial Thermal Therapy, LITT) to treat low-risk native prostate cancer. It is an open, single centre (Laser Prostate Centres of America, Houston, Texas), non-randomized, uncontrolled interventional study.

Due to the newness of the FLA technique, medical centres are inclined to have an extensive post treatment surveillance protocol. One such protocol requires within 3 to 6 months of treatment:

A digital rectal examination (DRE)

A PSA test

A PCA3 Test (this requires the prostate to be massaged during the DRE)

An mpMRI-guided targeted biopsy (probably one or two needles only).

If no residual disease is present, these tests will be repeated one year later with the exception of a targeted biopsy of the region of interest and a 12-core random biopsy will be performed, both done under TRUS guidance. Thereafter, all of the tests with the exception of mpMRI, will be performed every six months. The mpMRI will be performed every two years.[6]

FLA is still considered in the USA and Europe as a treatment under investigation. An international multi-disciplinary panel of 48 experts agreed on a standardised study design for future clinical trials for FLA. Their focal trial design standards were:

Patient inclusion: PSA <15 ng/ml, clinical stage T1c-T2a, Gleason 3+3 or 3+4, life expectancy >10 years, and any prostate volume

Post-treatment evaluation: TRUS biopsies taken between 6 and 12 months after treatment

Primary objective: focal ablation of clinically significant disease with negative biopsies at 12 months after treatment as the primary endpoint.

What is beyond belief is the absence of any reference to mpMRI in their design standards. This latter technique is rapidly revolutionising focal therapies for the treatment of prostate cancer. What can perhaps be deduced by this omission is the conservatism of many urologists, and the possible protection of ‘their patch’ (biopsies to be done by urologists and not by radiologists)!

Who is a Candidate for Focal Laser Ablation of the Prostate?

Men are diagnosed with either unifocal or multifocal prostate cancer. Unifocal cancers exist in one lobe of the prostate only. These cancers are ablated which leaves the rest of that lobe (consisting of healthy tissue) and the other lobe unaffected by the treatment. It is obvious that the ideal candidate for this procedure is an individual who places a high priority on preserving sexual function. Further, he should have a single prostate region of interest (one prostate lobe only) as shown on the mpMRI that is confirmed by biopsy to be low or intermediate prostate cancer. Men with multifocal (both lobes) low-risk cancer unrelated to a region of interest may also be possible candidates, dependant on their data. The European Urology Association Guidelines on Prostate Cancer Update April 2014, include quite different selection criteria for focal therapies.[7] The guidelines also state: “Focal therapy of any sort is investigational, and the follow-up and retreatment criteria are unclear.” Editor’s Note: The above EUA Guidelines make no reference to FLA. They only refer to two foci treatments: HIFU and CSAP (Cryosurgery of the Prostate). They are very comprehensive and you might find it easier to ready the pocket version.[8]

In the Journal of Vascular and Interventional Radiology, Volume 30, Issue 3, March 2019, Eric Walser, MD., et al. (University of Texas Medical Branch at Galveston) asked the question: Can FLA of low to intermediate risk prostate cancer men preserve sexual and urinary function with low morbidity while providing adequate oncologic outcomes?

His research group of 120 men with low or intermediate risk cancer were subjected to FLA under MRI guidance. Median PSA was 6.05 ng/mL. Median follow-up period was 34 months (range, 17–55 months). Gleason score was 3+3=6 in 37 (30.8%), 3+4=7 in 56 (46.7%), and 4+3=7 in 27 (22.5%) patients. Tumour stage was T1c in 89 (74.2%), T2a in 26 (21.7%), and T2b in 5 (4.2%)

patients. Twenty (17%) patients had additional oncologic therapy 1 year after FLA when biopsy confirmed cancer following abnormal MR imaging. Median PSA decreased to 3.25 at 12 months.

One year after FLA, selected patients had low morbidity, no significant changes in quality of life, and 83% freedom of re-treatment rate. Sexual and urinary function did not significantly change after FLA.

FLA as a salvage or recurrent prostate cancer treatment

FLA is an excellent modality when combined with mpMRI for the detection and treatment of recurrent prostate cancer. All prostate cancer treatments (excluding active surveillance) see a percentage of patients go on to have a biochemical recurrence of their cancer. Even after a prostatectomy in which the entire prostate and seminal vesicles are removed, some cancer cells might remain that over time manifest themselves in the form of a continuous rise in PSA value.

It is difficult to detect recurrent tumours due to their generally small size and due to dramatic changes in the prostate itself after radiation or focal treatment. The benefit that FLA presents when used in conjunction with a 3T mpMRI system, is that the cancers can be identified and successfully ablated under MRI guidance. Side effects are generally less than those experienced with a salvage prostatectomy. Erectile dysfunction and urinary incontinence are rarely experienced when the procedure is undertaken by an experienced surgeon who has performed many such FLA and mpMRI salvage procedures. The salvage procedure that is generally followed is similar to that which would be undertaken during an initial diagnosis and treatment using FLA with mpMRI:

mpMRI scan identifies any areas of interest.

An MRI targeted biopsy or TRUS guided biopsy using computer co-registration is performed to confirm that the region/s of interest is/are cancerous.

A 3D Colour Doppler Ultrasound is also usually done to evaluate blood flow in the tumour area; tumour volume, size, tissue density and exact shape; location of the neurovascular bundles, etc.

The tumour/s located is/are ablated under MRI guidance. A small safety margin external of the tumour is also ablated.

Should a biopsy be done prior to the mpMRI scan, the alignment of the cancer in the biopsy cores is checked against the areas of interest identified by the mpMRI scan. A good match confirms prostate cancer at that location. FLA when used with mpMRI is likely to come into the main stream of prostate cancer therapy in coming years.

Summary – FLA

Probably the newest approved treatment for prostate cancer. FLA has begun to come into its own as a serious treatment, due mainly to the impact of mpMRI imaging. Its impact for the detection of tumours and then guidance in their destruction via FLA (or HIFU) is very significant.

FLA takes full advantage of the significantly higher detection level of tumours by MRI targeted biopsies compared with standard biopsy methods.

Individuals who places a high priority on preserving sexual function should seriously consider FLA under MRI guidance.

FLA of soft tissue only is FDA approved.

The technique is becoming more and more a treatment of choice demanded by patients. The urology profession is responding to this demand with more centres starting to offer this method of treatment.

Some Factors in favour of FLA

It is minimally invasive, with patients feeling no pain and go home shortly after the one-hour procedure is completed.

Patients generally maintain a high degree of sexual function and incontinence is uncommon

It can be used as a primary or salvage treatment. It does not limit re-treatment with FLA or any other treatment protocol should the cancer progress elsewhere in the prostate.

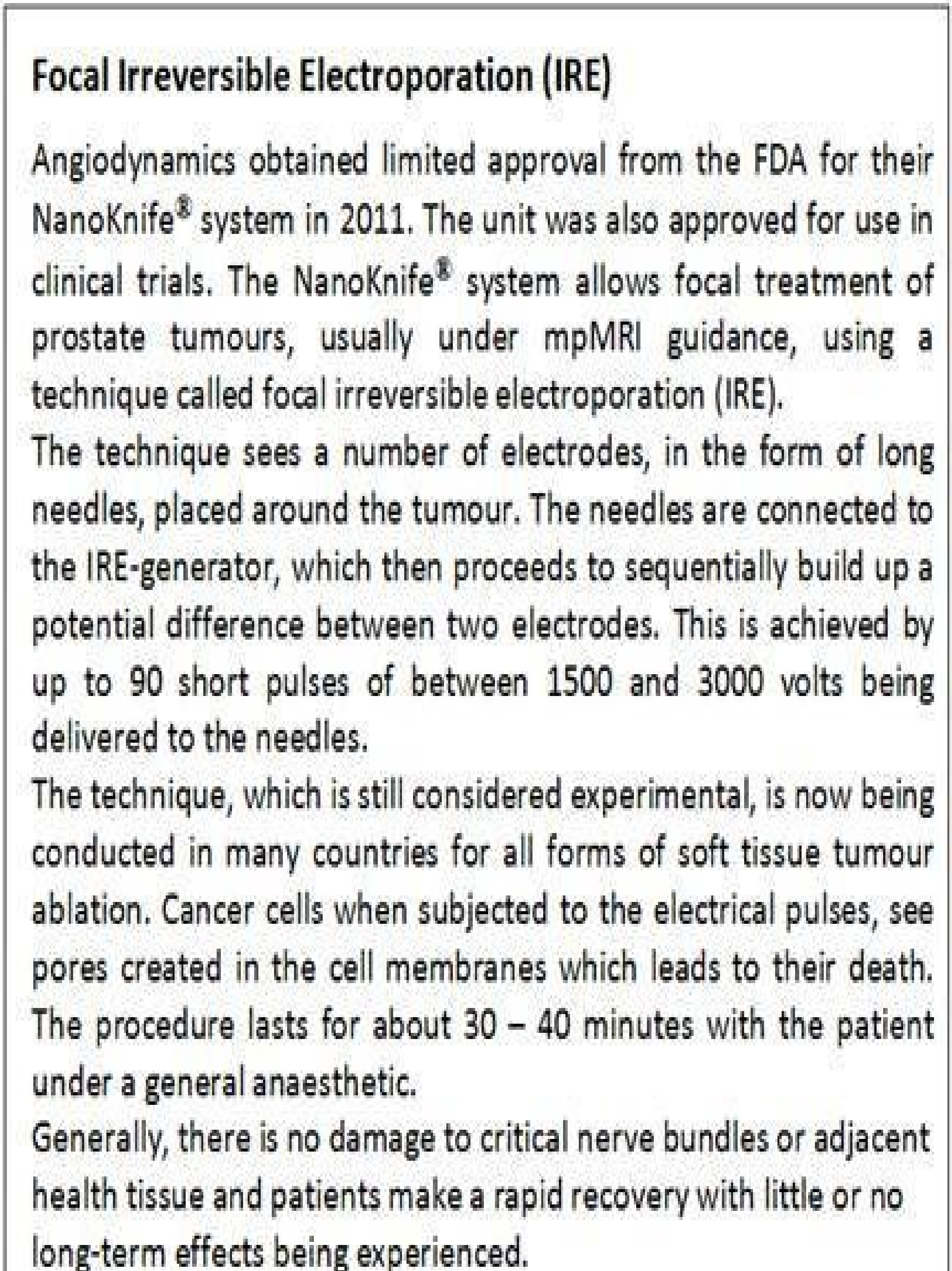
Some Factors against FLA

Whilst now extensively available in the USA, FLA of the prostate is still not FDA approved and most health funds do not cover the procedure.

With any new technique, it takes time for long term data to become available to conclusively prove the viability of the methodology. This, coupled with the general conservatism of the urology profession, delays the widespread uptake of techniques like FLA combined with mpMRI.

Possible inexperience of urologists in mastering the technique.

It is generally suitable for low and intermediate risk patients only.



Focal Irreversible Electroporation (IRE)

Angiodynamics obtained limited approval from the FDA for their NanoKnife® system in 2011. The unit was also approved for use in clinical trials. The NanoKnife® system allows focal treatment of prostate tumours, usually under mpMRI guidance, using a technique called focal irreversible electroporation (IRE).

The technique sees a number of electrodes, in the form of long needles, placed around the tumour. The needles are connected to the IRE-generator, which then proceeds to sequentially build up a potential difference between two electrodes. This is achieved by up to 90 short pulses of between 1500 and 3000 volts being delivered to the needles.

The technique, which is still considered experimental, is now being conducted in many countries for all forms of soft tissue tumour ablation. Cancer cells when subjected to the electrical pulses, see pores created in the cell membranes which leads to their death. The procedure lasts for about 30 – 40 minutes with the patient under a general anaesthetic.

Generally, there is no damage to critical nerve bundles or adjacent health tissue and patients make a rapid recovery with little or no long-term effects being experienced.

Chapter 13.

Hormone Therapy

It has long been known that testosterone, a male hormone that is produced by the testicles, is involved in stimulating the further development of cancer cells in the prostate after the cancer has started. Before looking at the various hormone therapy options, let’s look at a few definitions and statements that will make the treatments outlined more understandable:

Hormones are biochemical substances that are made in glands in the body. They affect the action of cells and tissue in the human body and reach their target areas mainly via the bloodstream.

Androgens are male sex hormones and are a class of hormones that control the development and maintenance of male characteristics.

Testosterone and dihydrotestosterone (DHT) are the two most abundant androgens in men. Almost all testosterone is produced in the testicles; a small amount is produced by the adrenal glands. Prostate cancer cells also have the ability to produce testosterone.

Hormone therapy, also called androgen deprivation therapy (ADT) or androgen suppression therapy (AST) is a powerful form of anti-cancer treatment in that it inhibits the production of androgens, blocks androgen action, or both. Hormone therapy can slow prostate cancer cell growth, which is stimulated by androgens.

Androgens are necessary for normal growth and function of the prostate. They are also necessary for the growth of prostate cancer cells.

Early in their development, prostate cancers need relatively high levels of androgens (mainly testosterone and DHT) to grow. Such prostate cancers are referred to as androgen dependent or androgen sensitive because treatments that decrease androgen levels or block androgen activity can inhibit their growth. Current hormone therapy treatments do one of three things:

They block the production of androgens throughout the body

They block the action of androgens in the body

They reduce androgen production by the testicles.

Treatments that reduce androgen production by the testicles are the most commonly used hormone therapies for prostate cancer.

Orchiectomy is a surgical procedure to remove both testicles, in cases of prostate cancer. This radical treatment is called surgical castration and is permanent and irreversible. The level of testosterone in the blood usually drops to about 10% of the previous level after the surgery. It is done only occasionally today as the same outcome can be achieved biochemically.

Drugs called luteinizing hormone-releasing hormone (LHRH) agonists, prevent the secretion of a hormone called luteinizing hormone. The LHRH agonist is a drug that is usually implanted by injection under the skin. Treatment with a LHRH drug is referred to as medical castration or chemical castration. It works by lowering the androgen levels in the body to the same extent as an orchiectomy. It offers one major advantage over an orchiectomy in that its effect is reversible. Once treatment is stopped and the drug leeches out of the body, androgen production usually resumes.

What is testosterone flare or tumour flare? The LHRH drug briefly causes the pituitary gland to secrete extra luteinizing hormone, before it blocks its release. This flare in advanced prostate cancer patients can manifest itself in increased bone pain, bladder obstructions or spinal cord compression.

Names of some approved LHRH agonists are:

Goserelin - Zoladex® - (Astra-Zeneca)

Histrelin - Supprelin La®; Vantas® - (Endo Pharma.)

Leuprolide - Eligard®; Lupron® - (Sanofi; Abbott)

Triptorelin -Trelstar® -(Actavis Pharma.)

Leuprorelin- Lupron® - (Abbott Labs, et al.)

Buserelin- SupraFact® - (Sanofi).

LHRH and GnRH agonists are used to treat advanced prostate cancer. They are often used with other treatments, such as surgery or radiation therapy and are also used to relieve pain caused by metastatic prostate cancer.

A minor word of caution: In 2018, scientists at the Cedars-Sinai Hospital, Los Angeles, found that ADT sometimes promotes the transformation of prostate cancer cells into a more aggressive type, which is resistant to treatment. Their study indicated that a possible reason for this resistance, was that ADT causes some adenocarcinoma cells to become neuroendocrine cancer-type cells - a rare type that normally appears in fewer than one percent of prostate cancer patients. Published research suggests a quarter of the patients who receive ADT may relapse with tumours that show features of neuroendocrine prostate cancer and develop treatment-resistant disease, which is also called refractory prostate cancer.

“This transformation is a problem because neuroendocrine prostate cancer is especially aggressive, metastasizes more readily and is more resistant to both androgen-targeted therapy and chemotherapy,” explained Neil Bhowmick, PhD, co-director of the Cancer Biology Program at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai.

The researchers examined the interactions between the tumour epithelia and its micro-environment and how cancer cells interact with the non-cancerous supporting cells near the tumour. These interactions, they noted, raised the level of the amino acid glutamine, turning the supporting cells into ‘factories’ that supplied fuel for the cancer cells. Glutamine is the most abundant amino acid in the blood and tissues. It is essential for tumour growth.

Research is ongoing to develop a simple blood test measuring glutamine that might predict when ADT resistance would occur.

Drugs called LHRH antagonists, which are another form of medical castration. LHRH antagonists (sometimes called gonadotropin-releasing hormone or GnRH antagonists) work by preventing LHRH from binding to its receptors in the pituitary gland. This action stops the secretion of luteinizing hormone, which cause the body’s androgen levels to drop to orchiectomy levels. LHRH antagonists are often preferred to LHRH agonists in advanced prostate cancer patients as they do not cause a testosterone flare. One LHRH antagonist, degarelix (Brand Name Firmagon® – Ferring Pharma.), was approved in late 2008 to treat advanced prostate cancer in the United States. It is given by injection.

Estrogens are hormones that promote female sex characteristics. They are able to inhibit androgen production by the testicles, but are seldom used today for prostate cancer because of their side effects and the better efficacy of other drugs.

Treatments that block the action of androgens in the body include anti-androgens. They are drugs that compete with androgens for binding to the androgen receptor. They reduce the ability of androgens to promote prostate cancer cell growth. As anti-androgens do not block androgen production, they are mainly used in combination with orchiectomy or an LHRH agonist. Use of an anti-androgen drug in combination with orchiectomy or an LHRH agonist is called combined androgen blockage, complete androgen blockade, or maximal androgen blockade.

Anti-androgens that are approved in the United States to treat prostate cancer include:

Flutamide (Brand Names: Flutamin®, Eulexin®) Manufacturer: Merck & Co.

It competes with testosterone and its powerful metabolite, dihydrotestosterone (DHT) for binding to androgen receptors in the prostate gland. By doing so, it prevents them from stimulating the prostate cancer cells to grow. Apparently, it is less used now, due to its side effects.

Prof. L. Klotz (University of Toronto Division of Urology) reported at EMUC19 on a Phase 2b trial where Liproca® Depot combines NanoZolid® (a slow drug release agent) with 2-hydroxyflutamide (a well-established anti-prostate cancer drug) over periods of potentially more than six months. Liproca® Depot's target group is patients under Active Surveillance (AS) with intermediate risk of cancer progression. Initial results are very promising, with Liproca ® Depot likely to fill a huge unmet need for AS patients.

Enzalutamide (Brand: Xtandi®) Made by: Medivation and Astellas

This was approved as a second-generation therapy for metastatic castration-resistant prostate cancer (mCRPC) treatment in August 2012. This approval needed patients to have been previously treated with docetaxel. In the clinical trial leading up to the approval of Xtandi by the FDA, 0.9% of patients taking Xtandi during the trial were reported to suffer a seizure. The withdrawal of Xtandi saw the seizures disappear. The trial reported overall median survival rate of 18.4 months on Xtandi versus 13.6 months with patients on the placebo. Clinicians are excited about the potential of this new drug class.[1] In September 2014, the FDA approved it for use in men with metastatic CRPC who have not received chemotherapy. The approval was based on the results of the Phase 3 PREVAIL trial, which ended early after outstanding results were obtained.

My brother was prescribed Xtandi in January 2016 for his metastatic CRPC. His PSA dropped from about 20 ng/ml to less than 9 within three weeks of starting to take the drug. Further reductions followed. He has experienced no side effects other than extreme drowsiness which has restricted his abiity to drive. He has had to half his dosage to ensure he can drive safely. A downside of this treatment is the extremely high cost of the drug: more than US$5000 for a three-week supply. Fortunately, its cost is covered by our Pharmaceutical Benefits Scheme in Australia and by insurance in some other countries. See details of the EnzaMet and other trials on page 197.

Bicalutamide (Brand Names: Casodex®, Cosudex®) Manufacturer: AstraZeneca

It was originally launched as a combination therapy for metastatic prostate cancer patients. Subsequently, it was launched as a monotherapy for earlier stage prostate cancer. Most advanced prostate cancer patients eventually become resistant to anti-androgen including bicalutamide therapy. Anti-androgens are usually taken in tablet form.

Treatments that block the production of androgens from the adrenal glands and prostate cancer cells include:

Drugs called Androgen Synthesis Inhibitors (ASI). They block testosterone production by inhibiting an enzyme called CYP17 (cytochrome P450 17 alpha-hydroxylase). This enzyme, which is found in all three testosterone production sources in the body (testes, adrenal glands and cancer cells), plays a key role in allowing the body to produce testosterone from cholesterol. The adrenal glands and the prostate cancer cells produce enough androgens to support ongoing cancer cell growth. The use of an ASI reduces the testosterone levels to the lowest level possible.

Approved drugs include:

Cabazitaxel (Brand Name: Jevtana®) Manufacturer: Sanofi-Aventis. It is usually prescribed together with prednisone to treat mCRPC after chemotherapy treatment with docetaxel (Brand Names: Taxtore®, Docefrez®) Manufacturers: Sanofi; Sun Pharmaceutical.

Sipuleucel-T (Brand Name: Provenge®). Manufacturer: Dendreon Corporation.

Further details on Provenge® are included in the next chapter as it is an immunotherapeutical rather than a true ASI. Sipuleucel-T was the first therapeutic cellular immunotherapy to demonstrate effectiveness in Phase 3 clinical trials by prolonging the life of patients who have advanced to the late stage of the disease with mCRPC - which is sometimes called asymptomatic Hormone-Refractory Prostate Cancer (HRPC). It is specifically prepared using harvested dendritic cells from the patient's white blood cells, which are incubated with a two-part fusion protein. The resultant blood product is returned to the infusion centre for re-infusion into the patient. This re-infusion leads to an immune response against cancer cells carrying the PAP antigen. This very expensive treatment, outlined by Philip W. Kantoff, et al. after a Phase 3 clinical trial, was shown to prolong life with a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group verses 21.7 months in the placebo group.

Dendreon Pharmaceuticals, the manufacturers of Provenge®, in September 19, announced the publication of results from its PROCEED registry study (NCT01306890), which evaluated real-world use of sipuleucel-T in 1976 men with asymptomatic or minimally symptomatic mCRPC. The findings, published in Cancer [2], showed that men with mCRPC who were treated with sipuleucel-T when their PSA was < 5.27 ng/mL had a median survival of nearly four years. Median survival was found to be:

Baseline PSA < 5.27 ng/mL – 47.7 months

Baseline PSA > 5.27 to ≤ 15.08 ng/mL – 33.2 months

Baseline PSA > 15.08 to ≤ 46 ng/mL – 27.2 months

Baseline PSA > 46 ng/mL – 18.4 months.

Findings from the PROCEED registry are consistent with a previous post-hoc analysis of the pivotal Phase 3 IMPACT trial of sipuleucel-T published in Urology in 2013. In that analysis, a lower baseline PSA level was associated with improved overall survival (OS). Among patients with a baseline PSA ≤22.1 ng/mL, the median OS was 41.3 months (3.4 years) for those treated with sipuleucel-T vs. 28.3 months for those in the control arm – an improvement of 13 months.

Abiraterone Acetate (Brand Names: Zytiga® - Janssen Biotech Inc., Abretone® – Cadilla Pharmaceuticals, Yonsa® -Sun Pharmaceuticals and Churchill Pharmaceuticals).

It is used to prolong the life of patients with late-stage mCRPC whose prostate cancer is not responding adequately to androgen deprivation, or treatment with anti-androgens. In Phase 3 clinical trials, it was found to extend patient life by 14.8 months versus 10.9 months for the placebo group.[3] It is now FDA, EMA and MHRA approved for both mCRPC and metastatic hormone-naïve prostate cancer. In Australia it is TGA approved and is on the Pharmaceutical Benefits Scheme when used in combination with prednisone/prednisolone (these are cortisteroids, which are added to minimize the effect of abiraterone on other steroid pathways). It presents a host of side effects which need careful discussion with a medical practitioner. In 2018, the FDA approved Yonsa®, a new formulation of abiraterone for mCRPC.

Enzalutamide and abiraterone acetate (discussed above) have attracted considerable interest from the cancer research community and hardly a day passes without one or more scientific papers being published on their performance. Numerous trials have shown or are likely to show (when they finally report), significant increases in longevity versus their placebos. One such result was the PROSPER Phase 3 trial that concluded in 2018 that enzalutamide had a significantly longer time to metastasis (36.6 months) compared to placebo (14.7 months). Some therapies that claim to re-sensitize enzalutamide after the cancer progresses, are under investigation to confirm their efficacy in this situation.

I met an attendee at a support group meeting some months ago who had been on enzalutamide for almost 3 years with his present PSA down to 0.2. Fantastic. As is always the case with cancer, one or both these drugs (Xtandi and Zytiga) are ineffective or only work for a short time with some patients.

Late-stage prostate cancer patients, who are positive for the AR-V7 (androgen receptor splice variant-7) protein, a predictive and prognostic biomarker that signals that a patient has become resistant to androgen synthesis inhibitors like Xtandi®, Zytiga®, Erleada® or darolutamide. If the test detects AR-V7-positive tumour cells circulating in the blood of a patient with advanced prostate cancer, it means the patient has built resistance to these commonly used ASI therapies and should either switch to chemotherapy or start another type of therapy, which has been shown to prolong survival.

It is vital to find the most effective treatment for men with mCRPC without wasting time on therapies that are sub-optimal. The Oncotype DX AR-V7 Nucleus Detect test helps your medical team accurately determine the next treatment step. See Appendix 3 for more details.

We generically refer to prostate cancer as one disease, but speak to any urologist or oncologist and they will tell you that it presents itself in many ways. Dr. Charles ‘Snuffy’ Myers, prostate cancer survivor and recently-retired world-famous medical oncologist said, “Prostate cancer is like golf. You need to play it as it lies. Because the disease is variable, each treatment solution requires a unique strategy."

In the scientific literature, prostate cancer has been presented as existing in up to 28 different forms. About 90% of patients diagnosed with prostate cancer have acinar adenocarcinoma. Other types of adenocarcinoma include atrophic, foamy, colloid and signet ring carcinoma which are often treated the same way. Other formats include ductal adenocarcinoma, urothelial cancer, squamous cell cancer, and two types of cancer that originate in the neuroendocrine system (nerves and glands cells) being carcinoid and small cell tumours.

It is worth noting that a 2018 study showed that within 4 months of FDA approval of immunotherapies for treating various metastatic solid cancers, over 60% of eligible patients received immunotherapy. Oncologists have suggested that the use of chemotherapy is, in many cases, becoming the exception, rather than the norm.

Newest Generation Androgen Receptor Inhibitors

Apalutamide (Brand Name: Erleada®. Erlyand®) Manufacturer: The Janssen Pharmaceutical Companies of Johnson & Johnson.

Apalutamide is an androgen receptor inhibitor prescribed for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC). Like enzalutamide, it prevents the translocation of the androgen receptor to the nucleus and it inhibits interaction with DNA. In February 2018, it became the first treatment to receive FDA approval for nmCRPC. The SPARTAN trial, which preceded the FDA approval, showed the most common adverse reaction was a rash appearing some months after treatment started. Less common were fatigue, hypertension, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema. Some of these might see darolutamide being considered as an alternative, possibly offering lesser side effects.

It has since been included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a treatment option for patients with nmCRPC (M0) with a category 1 recommendation (especially for those with a PSA doubling time ≤ 10 months). Patients with a history of seizures, with severe cardio-vascular disease, and frail patients at high risk of falls are NOT candidates for apalutamide and enzalutamide. See Appendix 3 for more details and NCCN Guidelines acknowledgement.

Additionally, the American Urological Association (AUA) Guidelines for Castration-Resistant Prostate Cancer (CRPC) were updated to include apalutamide (Erleada®) with continued ADT as a treatment option that clinicians should offer to patients with asymptomatic nmCRPC. It is included as one of the options clinicians should offer to patients with nmCRPC who are at high-risk for developing metastatic disease (Standard; Evidence Level Grade A). See Appendix 3 for more details and AUA Guidelines acknowledgement.

In January 2019, the TITAN Phase 3 study for men with newly-diagnosed mCRPC and who were also under ADT, was ‘unblinded’ as the two endpoints of the study had been met (significantly improving radiographic progression-free survival (rPFS) and overall survival (OS).

Adding apalutamide to ADT reduced the risk of death by 33% in patients with mCRPC compared with ADT alone, according to top line results from the TITAN Phase 3 trial presented at the 2019 ASCO Annual Meeting. Results of the trial, which were also published in the New England Journal of Medicine, showed that at a median follow-up of 22.7 months, the 2-year overall survival (OS) rate was 82.4% in the apalutamide arm compared with 73.5% in patients receiving ADT alone. The median OS was not yet reached in either arm. The addition of apalutamide also significantly reduced the risk of radiographic progression or death by 52%. The median radiographic progression-free survival (rPFS) was not reached in the apalutamide arm compared with 22.1 months in the control arm. The 2-year rPFS rates were 68.2% versus 47.5%, respectively. The OS and rPFS benefits were observed across patient subgroups.

Based on the TITAN data, a supplemental new drug application has been submitted to the FDA for the approval of apalutamide for use as a treatment of patients with mCRPC. In September 19, the FDA approved apalutamide for the treatment of mHSPC.

Darolutamide (Nubeqa®) Manufacturers: Orion, Bayer HealthCare

Darolutamide is a structurally unique androgen receptor antagonist. It is the latest in the range of next-generation AR inhibitors. It has shown strong activity and minimal toxicity in Phase 1 and 2 trials ARADES (Fizazi, Lancet Oncol 2014) and ARAFOR (Massard, Eur Urol 2016). It is currently being evaluated in the ARAMIS Phase 3 trial for men with non-metastatic CRPC.

In contrast to enzalutamide, darolutamide does not significantly penetrate the blood-brain barrier which may reduce the risk of fatigue, cognitive impairment, and seizure. It prolongs metastasis-free survival and decreases the risk of pain progression in men with nmCRPC, without adversely affecting quality of life, according to study findings presented at the 2019 Genitourinary Cancers Symposium.

“This is really a very safe drug as far as we can tell,” said lead investigator Karim Fizazi, MD, PhD, of Institut Gustave Roussy, Université Paris-Sud, Villejuif, France.

The metastasis-free survival found with darolutamide (40.4 months vs 16.2 months with placebo) in the ARAMIS trial is similar to that observed with enzalutamide in the Phase 3 PROSPER trial (36 months for enzalutamide vs 14.7 months for placebo) and apalutamide in the Phase 3 SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) trial (40.4 months for apalutamide vs 16.2 months with placebo). Unlike enzalutamide and apalutamide, darolutamide was not associated with a higher risk of falls and fractures, which is probably due to central nervous system toxicity.

Another advantage is that darolutamide has been found to block the activity of all tested/well-known mutant androgen receptors, including the recently-identified clinically-relevant F876L mutation that produces resistance to enzalutamide and apalutamide.

In July 2019, the FDA approved darolutamide for men with nmCRPC. This approval follows the recent ASCO meeting in Chicago where Phase 3 trial results showed that darolutamide in combination with ADT delays ‘disease worsening’ in men with nmCRPC and stabilizes their quality of life, without increasing the incidence of adverse events.

Other Androgen Synthesis Inhibitors

A number of other drugs are also prescribed for late stage prostate cancer treatment, such as ketoconazole (Nizoral® - can cause liver problems) and aminoglutethimide (Cytadren® - skin rash is a common side effect). These are sometimes referred to as second-line treatments for prostate cancer as they are/were used to treat other forms of cancer.

Bipolar Androgen Therapy

The use of bipolar androgen therapy (BAT), involving rapid cycling between high and low serum concentrations, was found to be safe and resulted in responses and re-sensitization to enzalutamide in men with mCRPC who progressed after initial enzalutamide therapy, according to a December 2017 study whose results were published in Lancet Oncology.

"Clinically, metastatic CRPC that has progressed after enzalutamide treatment is minimally responsive to further therapy that inhibits androgen receptor signalling," wrote study authors led by Benjamin A. Teply, MD, of Johns Hopkins School of Medicine in Baltimore. "Theoretically, rapidly varying the androgen concentrations between the extremes of supra-physiological and near-castrate, a strategy termed BAT, provides insufficient time for CRPC cells to adaptively regulate androgen receptor concentrations," and thus may promote cancer cell death and prevent resistance.

The new open-label Phase 2 study tested BAT in 30 patients. Treatment consisted of intramuscular testosterone cipionate 400 mg every 28 days until progression, as well as continued luteinizing hormone-releasing hormone agonist therapy. After progression, men were re-challenged with enzalutamide.

Sequencing tumour samples and the germline have shown that defects in DNA repair genes are common in patients with mCRPC. Research have shown that BAT disrupts DNA re-licensing and produces DNA double-strand breaks in CRPC cells. Given the emerging data on DNA repair defects in prostate cancer and the mechanism of BAT, we postulated that men with such defects may be particularly susceptible to BAT. A participant (70 years old, Gleason 9, radical prostatectomy followed by salvage radiation therapy, followed by hormonal therapy - see Figure 1) in an ongoing trial showed a remarkable and durable complete response to BAT. His tumour sequencing result supported the hypothesis that patients harbouring mutations in DNA repair pathway genes may be particularly sensitive to BAT. (His tumour sequencing revealed the BRCA2 and ATM mutations. Both of these mutations were present in the germline).

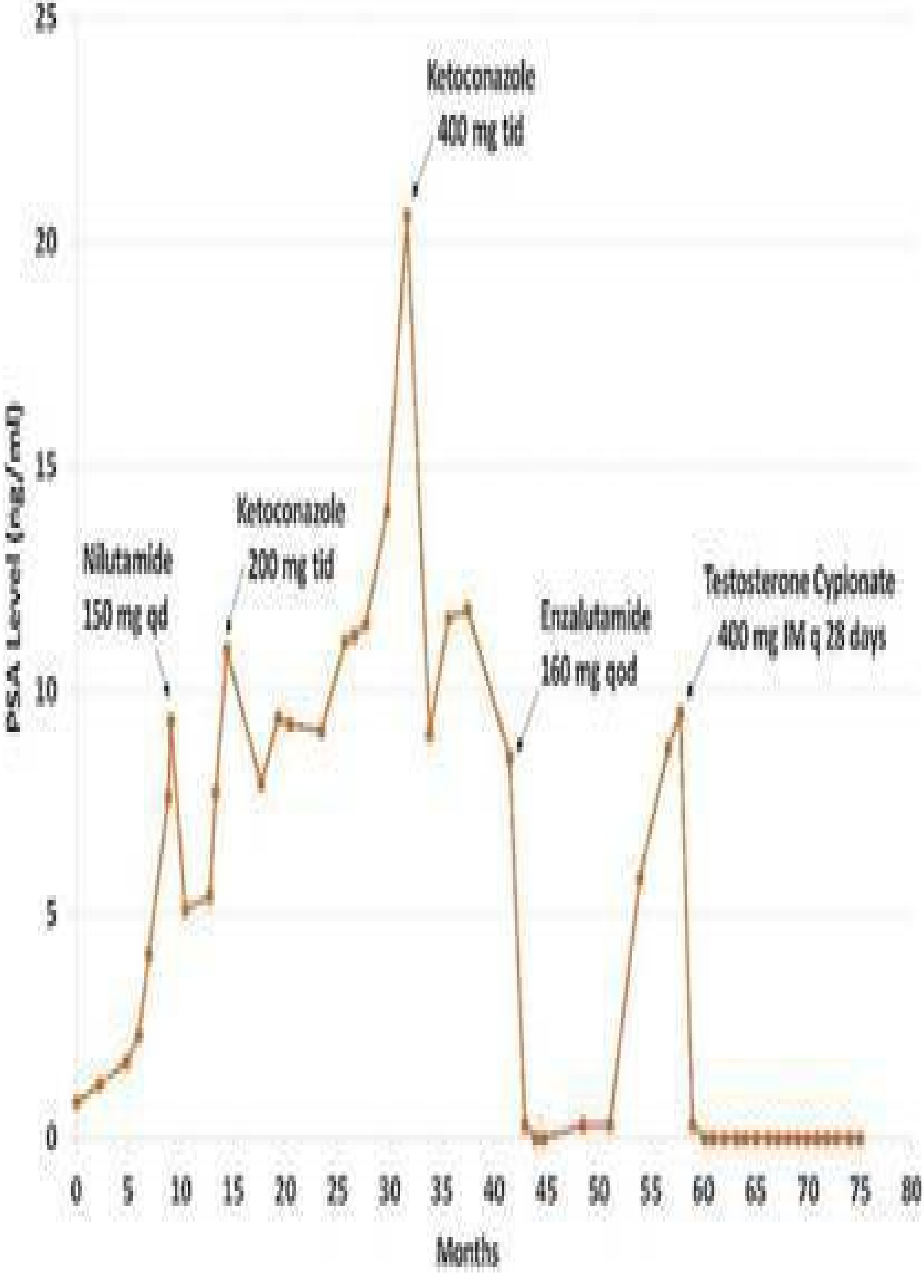

PSA Level (ng/ml)
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
Months
Nilutamide
150 mg qd
Ketoconazole
200 mg tid
Ketoconazole
400 mg tid
Enzalutamide
160 mg qod
Testosterone Cyplonate
400 mg IM q 28 days

Figure1. Prostate-specific antigen (PSA) levels over time in response to the hormonal therapies indicated. Extreme Response to High-dose Testosterone in BRCA2- and ATM-mutated Prostate Cancer. Teply, Benjamin A. et al. European Urology, Volume 71, Issue 3, 499

The RESTORE trial is evaluating BAT in men after abiraterone or enzalutamide failure. The co-primary end points were the response to BAT and BAT's response to a re-treatment with either abiraterone or enzalutamide. Early results from the enzalutamide arm have shown a >50% PSA decline and a measurable response in about one-third of patients. BAT was well tolerated with minimal side effects. On re-treatment with enzalutamide, about 50% of patients had a greater than 50% PSA response. BAT is also able to suppress AR-V7 expression in most men with detectable AR-V7 in their circulating tumour cell samples.

The TRANSFORMER trial includes 180 asymptomatic CRPC patients who have failed abiraterone. In the study, BAT is being compared to enzalutamide for the primary end point of progression-free survival. Patients are allowed to cross over following progression to the first therapy, with an important secondary end point being PSA progression-free survival on the second agent in order to evaluate the ability of BAT to re-sensitize tumours to androgen receptor sensitive inhibitors.

The mechanism of BAT inhibition is becoming more understood as research continues. Various pointers suggest that multi-therapies that might include BAT with PAPR inhibitors, platinum agents, proteasome inhibitors or immune checkpoint inhibitors might offer improved results.

Notwithstanding the above, it is very difficult to find medical oncologists and urologists who are firstly, up-to-date with the science behind BAT, secondly are prepared to prescribe testosterone and thirdly, well experienced in undertaking *this therapy and dealing with its pros and cons. So extreme caution should be the order of the day.*

Triple Androgen Blockade

Dr ‘Snuffy’ Myers, for years considered to be the US ‘doctor-to-see’ for men with progressing prostate cancer, practised what he called, Triple Androgen Blockade for men with metastatic prostate cancer. He outlined his therapy in his book, “Beating Prostate Cancer (Hormonal Therapy and Diet).” He prescribed Lupron, Casodex and Avodart (a 5-alpha reductase enzyme) to block AR activity. In more recent years (before he retired in 2018), he dropped Casodex and added Xtandi. It appears he also added metformin in some cases. Men on this regime reported excellent long-term results.

It appears that Dr Myers protocol was similar to that described in Dr Edward Friedman’s book “The New Testosterone Treatment: How You and Your Doctor Can Fight Breast Cancer, Prostate Cancer, and Alzheimer's.” I am aware of men that swear by Friedman’s work. One of these men with biochemical research experience, summarised the recommendations from the book as follows:

Take an aromatase inhibitor; don’t block the estrogen receptor – alpha as that would contribute to bone density challenges; block estradiol; take vitamin D3 and block MYC or glutamine by taking curcumin + resveratrol + ursolic acid. (The MYC oncogene is upregulated which increases glutamine metabolism).

The Likely Process When ADT Stops Working: Castration-Resistance

The oncologist prescribes a super-hormone like Zytiga® (abiraterone), Xtandi®

(enzalutamide), or Erleada® (apalutamide) or a chemotherapy drug like Taxotere® (docetaxel).

A blood sample is taken to determine which of the two types of therapy is most appropriate. The cancer cells in the blood are separated; these separated cells are tested to see whether the nucleus (centre) of these cancer cells, show the presence of a protein called AR-V7.

If a man did have AR-V7 in his cancer cell nucleus, he is called AR-V7-positive, if not AR-V7-negative. Clinical trials have shown that men who had AR-V7 lived longer if they started on a super-hormone rather than chemotherapy. Men who did not have AR-V7 lived longer if they started on chemotherapy, rather than a super-hormone.

PSMA lutetium-177 ligand therapy, is another treatment pathway as it becomes an ‘approved’ therapy by the regulatory authorities, within a year or so. See Chapter 8.7 for more details.

Intermittent Administration of Abiraterone

All mCRPC men on abiraterone will see their disease progress after a period of about 15 months. Some men might experience almost double this ‘average’ figure, but others see the disease progress earlier than ‘average’. Dr Robert Gatenby, MD, from the Moffitt Cancer Centre (MCC) reported on their work on the intermittent administration of abiraterone at the 25th Annual PCF Scientific Retreat in October 18. In their adaptive therapy trial, patients were given abiraterone until PSA levels dropped by ≥50%, at which time abiraterone treatment was discontinued. This was hypothesized to allow treatment-sensitive cells to re-populate the tumour and suppress growth of treatment-resistant cells. Abiraterone was administered again when a patient’s PSA level returned to the pre-treatment level (one cycle), and then withdrawn when the PSA was reduced to 50% of the pre-treatment value. Mathematical models predicted that tumour control with this approach could be maintained for 2 to 20 cycles of treatment.

In preliminary analysis of the first 18 patients enrolled by the MCC in this trial, the length of time between treatments ranged from 4 months to 1.5 years. The earliest disease recurrence in a patient was observed after 2 cycles. The longest survivors are still under treatment after 12 cycles (about 4 years). Thus far, four patients have experienced PSA and radiographic progression (at 12, 27, 30, and 32 months). However, the median time to progression for the treatment cohort has not yet been reached.

The MCC have generated mathematical models from patient data from the trial. Simulations using one patient’s data suggests that if abiraterone is stopped after the PSA drops 20% (below the starting PSA), cycle times could be shorter and tumour control could be maintained for almost twice the length of time. The mathematical simulations also predict that with concurrent therapy with abiraterone and docetaxel would increase time to progression four-fold. A randomised clinical trial is planned to support the validation of this treatment protocol.

Hormone Therapy and Side Effects

All hormone treatments for prostate cancer have side effects to a greater or lesser extent due to the reduction in male hormones in the body. These side effects are often drug specific. You should thoroughly discuss any proposed hormone therapy treatment with your medical specialist. You need to ask what side effects are likely with the treatment proposed. A different drug may present side effects that are more manageable to you whilst still providing an appropriate therapeutic performance. Side effects might include:

Erection problems (Erectile dysfunction)

Depending on the drug used and length of time it is taken will determine, whether or not erectile dysfunction will occur, in the short-term, longer term or permanently. An erection will not be possible, if you are taking luteinizing hormone (LHRH) agonists (sometimes referred to as LH blockers), such as Zoladex®, Prostap®, Lupron®, Trelstar®, etc. This is because LHRH agonists stop the production of testosterone by the testes. Once treatment ceases, erections may return over time, sometimes taking up to a year. Agonists appear to cause more erection problems than the anti-androgens such as bicalutamide and flutamide.

Hot flushes and sweating

The stopping of testosterone production by the body leads to the occurrence of bouts of hot flushes and sweating similar to that experienced by women during menopause. Should the extent and severity of these bouts become troublesome, your doctor can prescribe a drug to lessen the symptoms.

Loss of libido

Plain and simple, hormone treatment leads to a significant loss of libido (interest in sex). It cannot be fixed by a testosterone injection as the therapy is trying to starve the prostate cancer cells of access to testosterone. Taking anti-androgen drugs, like bicalutamide, make it more likely that erections and the libido are maintained.

Breast tenderness

Bicalutamide causes severe breast tenderness and some swelling when taken in high doses. Some doctors prescribe tamoxifen to reduce symptoms in severe cases. Other agonists and anti-androgens list breast soreness and swelling or growth as a potential side effect.

Testosterone flare (or tumour pain flare)

The LHRH drug briefly causes the pituitary gland to secrete extra luteinizing hormone, before it blocks its release. This flare in advanced prostate cancer patients can manifest itself in increased bone pain, bladder obstructions or spinal cord compression. Patients are often prescribed an anti-androgen when initiating a course of agonist treatment.[5]

Tiredness or weakness

There are a few things that can be done to counteract this tiredness:

Eat a healthy diet that will give you more energy

Don’t push yourself too hard and reduce any exercise regimens

Get support from family and friends

Rest up when feeling tired or fatigued.

Long Term Side Effects might include:

Mood swings

It is not uncommon to start feeling depressed about your prostate cancer situation and life in general. This feeling of depression might hang around for days or be rapidly replaced by feelings of well-being. If these mood swings are severe, the matter needs to be fully discussed with your doctor.

Bone thinning

Long term suppression of testosterone often leads to a lessening in bone thickness and density and the possibility of an increased risk of bone fractures. This is called osteoporosis. It can be treated by your doctor who may suggest Vitamin D, calcium or a more aggressive drug treatment.

Memory changes

It is not uncommon for men to complain of a reduction in memory recall after being on hormone therapy for some months. It is also harder to concentrate and the thought process is sometimes challenged. The memory is likely to return to previous levels after the hormone therapy has stopped and the drugs having leeched out of the body. Of course, hormone replacement therapy is not an option as suppression of testosterone levels is a vital step in fighting the prostate cancer.

Increased heart attack risk

Research suggests that there is a slight increase in the risk of a heart attack in men over 65 after taking hormone suppressors for more than 6 months. For this reason, your doctor may refer you to a cardiologist before commencing a course of long-term hormone treatment.

Weight gain

Some men find their weight increasing after some months on hormone therapy. The way to control this is exercise and diet. Easily written, but much harder to do in practice! Some testosterone suppressors have their own set of short- and long-term effects. Discuss these with your doctor.

Author's Note: The information outlined in this chapter is presented as a guide and it is no substitute for health care delivery by your medical team.

If you are taking ADT and have metastatic prostate cancer that is NOT castration-resistant, see details on the CHAARTED clinical trial in the next chapter.

What questions should I ask my doctor about hormone therapy?

Will hormone therapy alone cure my prostate cancer?

Do I start hormone therapy straight way or could it be delayed for a while?

How long is the hormone therapy course likely to take? Is it continuous?

Are you prescribing hormone therapy as a complement to another treatment? What is this other treatment?

How might hormone therapy affect my emotions?

What about my libido?

What side effects might I expect with what you are prescribing? Are any of the side effects likely to be permanent?

What about my ability to maintain an erection with the drug you are prescribing?

Is there treatment to restore my ability to maintain an erection during treatment or after concluding a course of hormone therapy?

How often should I have my PSA level check whilst undergoing hormone therapy?

How is the hormone therapy delivered and how often do I need to have it ‘topped up’?

Is it likely to affect my long-term fertility?

Summary – Hormone Therapy

Hormone therapy, also called androgen deprivation therapy (ADT), is a powerful form of medical castration and anti-cancer treatment in that it inhibits the production of androgens (the sex hormones), blocks androgen action, or both. Hormone therapy can slow prostate cancer cell growth, which is stimulated by androgens.

Treatments that reduce androgen production by the testicles are the most commonly used hormone therapies for prostate cancer. Drugs called luteinizing hormone-releasing hormone (LHRH) agonists, prevent the secretion of a hormone called luteinizing hormone. The most commonly used LHRH agonists are Zoladex® and Lupron®.

Drugs called LHRH antagonists, are another form of medical castration. LHRH antagonists (sometimes called gonadotropin-releasing hormone or GnRH antagonists) work by preventing LHRH from binding to its receptors in the pituitary gland. Firmagon® is the most common LHRH antagonist and is used in advanced cancer cases. Anti-androgens and androgen synthesis inhibitors complete the drug arsenal to fight late stage or hormone resistant prostate cancer.

Some Factors in favour of Hormone Therapy

It can be used as a monotherapy or in combination with other treatments like radiation.

Current hormone therapy treatments block the production and the action of androgens throughout the body. They reduce androgen production by the testicles.

A host of new drugs, used individually or in combination with other drugs or treatments, are available to extend life in metastatic prostate cancer cases.

Some Factors against Hormone Therapy

Side effects from hormonal treatment include erectile dysfunction, lack of libido, breast tenderness or growth, sweating, mood swings, bone thinning, increased heart attack risk, etc.

The Enzalutamide ENZAMAT Phase 3 Trial outcomes

ENZAMET is the first mHSPC trial to report OS data of enzalutamide plus testosterone suppression and outcomes if patients also received concurrent docetaxel. Enzalutamide (Xtandi), an androgen-receptor inhibitor, is used in the treatment of patients with mCRPC who have previously received docetaxel. It is also used with men with earlier nmCRPC.

Men with mHSPC experience a survival benefit with the addition of either docetaxel (see page 202), or abiraterone acetate (Zytiga) to ADT, with both approaches being current standards of care (SOC). Prior to the ENZAMAT clinical trial, it was not known whether adding enzalutamide to testosterone suppression, with or without early docetaxel, would improve survival in men with mHSPC.

In this open label, randomized, Phase 3 trial, patients were assigned to receive testosterone suppression plus either enzalutamide or a standard non-steroidal anti-androgen therapy. (An NSAA like bicalutamide, nilutamide, or flutamide). The primary end point was overall survival. Secondary end points included progression-free survival as determined by the PSA level, clinical progression-free survival, and adverse events.

The trial results are complex to interpret due mainly to the higher cancer burden of the docetaxel group. The trial found Xtandi improve survival when not competing with docetaxel and in patients with mostly low-volume disease. The enzalutamide group had a higher incidence of seizures and other toxic effects, especially among those treated with early docetaxel.

Enzalutamide significantly improved overall survival (OS) in comparison with a conventional NSAA when both were added to SOC in this setting, reported lead author Christopher Sweeney, MD, of Dana Farber Cancer Institute, Boston, Massachusetts. Sweeney summarized that enzalutamide plus SOC "*represents an appropriate option for men with metastatic prostate cancer commencing testosterone suppression.*"

What about taking Enzalutamide (Xtandi) plus Abiraterone Acetate (Zytiga) at the same time?

Two eggs are better than one said the chef. So, researchers thought it appropriate to determine if two therapies indeed were better than one alone, as the above drugs offer similar AR responses, but by a different mechanism.

Well, when it comes to mCRPC patients taking both drugs at the same time, a recent Phase 3 trial has shown conclusively that there is no significant patient benefit in doing so.

Enzalutamide's anti-androgen mechanism is through binding of the androgen receptor (AR), inhibiting nuclear translocation of AR and subsequent AR binding of DNA, whereas abiraterone's mechanism of action is through CYP17A inhibition, thus preventing androgen biosynthesis. An earlier study by Eleni Efstathiou, MD, showed that the enzalutamide with abiraterone acetate + prednisone combination was safe and well-tolerated for most patients, without significant drug-drug interactions. The more recent study by Morris et al., builds on that study by providing Phase 3 randomized data comparing the combination verses enzalutamide alone which provided similar results.

ARCHES: A Randomized, Phase 3 Study of ADT with Enzalutamide or Placebo in men with mHSPC.

ARCHES: is a multinational, double-blind, Phase 3 trial (NCT02677896), wherein 1,150 men with mHSPC were randomly assigned 1:1 to enzalutamide or placebo, plus ADT, stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-free survival. Enzalutamide plus ADT significantly reduced the risk of PSA progression, bone metastases, castration resistance, and reduced pain risk.

Conclusion: Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time versus placebo plus ADT in men with mHSPC, including those with low-volume disease and/or prior docetaxel, with a safety analysis that seems consistent with the safety profile of enzalutamide in previous clinical trials in castration-resistant prostate cancer.

Chapter 14.

Chemotherapy and Immunotherapy

We heard earlier that any prostate cancer diagnosed after a biopsy would either be localised (Stage T1 or T2), advanced localised (again Stage T1, but more likely to be T2) or metastatic (stage T3 or T4). Of course, the Gleason Score determined by the pathologist examining the biopsy samples, is a very important factor in evaluating the progression of the cancer. A T3 or T4 staging assessment is likely to see a Gleason Score of between 8 to 10 (however, it could be much lower), which suggests high risk cancer is present.

Author's Note: This book has been written to broadly assist fellow prostate cancer sufferers and their friends and family. It details my journey from diagnosis to a cure (or remission). It also is a compendium of notes of current and future practice in diagnosing and treating prostate cancer. It has been prepared after a very extensive search of the research literature, company product information, books on prostate cancer, anecdotal information from other prostate cancer survivors, etc. However, I am NOT a doctor or trained in medicine. THEREFORE, IT IS IMPERATIVE THAT ALL WHO READ THIS BOOK, DO SO REALISING THAT ITS CONTENT IS IN NO WAY A SUBSTITUTE FOR APPROPRIATE PROFESSIONAL MEDICAL ADVICE. The Author takes no responsibility for the accuracy or relevance of all or any specific content contained within the book whether it be stated or implied.

If you are diagnosed with prostate cancer of any Staging or Gleason Score, it is very important for you to fully engage with your medical specialists, to finalise a treatment or active surveillance regimen, which suits your unique circumstances. It is even more important to urgently finalise a treatment regimen with your medical specialist/s if your prostate cancer is T3 or T4. (Active surveillance is unlikely to be an option). Your urologist is likely to refer you for a bone scan, PET/CT scan and/or a MRI scan. Dependant on the results obtained, the urologist is likely to refer you to an oncologist, a doctor who specialises in treating cancer patients. The treatment that the oncologist might prescribe would be dependent on how far the prostate cancer may have spread. Has it reached the lymph glands and/or the seminal vesicles adjacent to the prostate or has it migrated to the pelvic bones or to other organs in the body, where secondary cancers might have formed? Note that prostate cancer cells that escape from the 'box', migrate in three ways: to surrounding tissue; into the lymph glands/nodes or vessels to other parts of the body (the human lymph system is another 'highway' like the blood system) or via the blood stream. Any secondary cancers that form elsewhere in the body after migration from the prostate have the same characteristics of prostate cancer.[1]

A T4 level cancer could have spread to the bladder, rectum, seminal vesicles, lymph nodes or pelvic bone, all of which are adjacent to the prostate. It could also have migrated to other organs of the body. Fortunately, there is a wide array of 'tools' available to your medical team to treat T3 or T4 cancer. These include hormone therapy, EBRT with or without hormone therapy, chemotherapy with hormone therapy. If the cancer is found in the bone, it is possible that bisphosphonate treatment might be recommended. Bisphosphonates inhibit a type of bone cell that breaks down bone and reduce the pain of bone cancer. It is sometimes called diphosphonate. Commonly used bisphosphonates [2] are:

Zoledronic acid (Zometo®) - taken as an intravenous drip

Disodium pamidronate (Aredia®) - taken as an intravenous drip

Ibandronic acid or ibandronate (Bondronat®) - taken as a capsule or an intravenous drip

Sodium clodronate (Bonefos®, Clasteon®, Loron®) - taken as a tablet or capsule

The list is completed by Denosumab (Xgeva®, Prolia®).

The bisphosphonates zoledronic acid and denosumab have been commonly prescribed for the prevention of bone injuries in men with mCRPC. However, studies of these compounds have not demonstrated a survival benefit. So, what is the role of bisphosphonates or denosumab in combination with the newish hormonal agents abiraterone acetate and enzalutamide, second-line chemotherapy cabazitaxel, and the radiopharmaceutical radium-223 dichloride (radium-223)? These latter compounds all offer improved overall survival benefits, which appear to be further enhanced by the addition of zoledronic acid or denosumab according to preliminary studies. Check with your medical oncologist.

In June 19, the manufacturer of Xgeva® (Amgen) announced the results of six clinical development studies that examined the effectiveness of dosage intervals in patients being treated for bone metastases (from patients with solid tumours). They concluded that a dose of 120mg administered every 4 weeks provided the best direct effect of Xgeva® on bone resorption thus minimising skeletal-related events.

Chemotherapy is often prescribed if hormone therapy becomes ineffective. This situation generally occurs when the cancer cells no longer need testosterone to grow. They are said to have reached a castrate-resistant, hormone-resistant or hormone-refractory state (all the same). Chemo, as it is referred to in short, is usually a cycle of drugs that are administered by intravenous drip as a hospital outpatient. These cycles vary, but usually extend for two or three weeks, after which the chemo is stopped for a similar length of time, to allow the normal body cells to recover from the often-harsh action of the chemotherapy.

Today, there is a whole host of drugs that are used to fight prostate cancer. The more modern drugs are more likely to have less unpleasant side effects and better efficacy than older drugs – they are inclined to extend life and improve the quality of life. The University of North Carolina at Chapel Hill in 2016 announced a research breakthrough in this regard. The chemotherapy drug called paclitaxel (Taxol®) was inserted in ‘immune bubbles’ or exosomes that were produced from the patient’s own white blood cells.

Their innovation prevents the destruction of the drug by the immune system and so delivers far more of the drug’s active agent to the tumour, thus delivering all the benefits at much lower doses, with far less side effects. This is particularly impressive as Taxol® is considered to be a ‘high side effects’ drug. The research showed that 50 times less of the drug provided the same results with fewer and milder side effects. The exact mechanism as to how the exosomes do their work is still unclear, but it is known that they swarm the cancer cells, completely bypassing any drug resistance they may have and deliver their full payload to the tumour. See Chapter 22 for details of the Starpharma dendrimer technology that delivers ‘comparable’ results using a completely different approach.

Docetaxel (Brand Name: Taxotere® or Docecad®) Generic

The usual initial chemo drug of choice is docetaxel usually given with the steroid drug prednisone. It works by disrupting the normal function of microtubules (the cell cytoskeleton) and thereby stopping cell division. Docetaxel has helped many men survive beyond five years. It is clear that docetaxel slows metastatic cancer progression and can lead to disease-free survival. Conjunctive treatment of prednisone with docetaxel has been shown to lead to improved survival rate, as well as improved quality of life and reduction of pain compared with other treatments like mitoxantrone.

Most patients taking docetaxel, find that their side effects are significantly reduced by fasting (vegetable broth and an energy drink only) for 48 hours before chemo. Discuss this with your oncologist.

Cabazitaxel (Brand Name: Jevtana®) Manufacturer: Sanofi

If the docetaxel does not work (or becomes ineffective), a drug called cabazitaxel (CBZ) often heads the list of the next chemo drug to be tried. This drug is usually administered with Neulasta which boosts the white cell blood count, thus supporting the immune system when it is under stress from the drug. Most of these drugs work by identifying fast dividing cells and attacking them. Unfortunately, the normal cells of hair follicles, the lining of the mouth and intestines, and the bone marrow are also fast dividers and are impacted by the drug. Side effects such as loss of hair, mouth ulceration, diarrhoea, nausea and fatigue ensue. An allergic reaction sometimes occurs in patients receiving either of these two chemo drugs. Doctors usually prescribe other medication to lessen the impact of possible allergies or side effects.

The Jetvana (CBZ) CARD trial (NCT02485691) reported in September 19. CBZ significantly improved clinically important patient outcomes including rPFS and OS vs androgen receptor-targeted therapies (ART) like Xtandi and Zytiga in patients with mCRPC previously treated with docetaxel and an alternative ART. CBZ was considered to be the preferred option in this setting.

Both docetaxel and cabazitaxel are drugs that are also under clinical trials when treated with the Starpharma dendrimer technology. These promise greater efficacy with significantly reduced side effects. See Chapter 22 for more details.

A very important clinical trial (ECOG E3805 CHAARTED) with docetaxel was concluded in 2015. This trial was conducted with 790 patients who had been newly diagnosed with mHSPC (cancer that has not reached the castration-resistant stage). The standard treatment for such patients was ongoing treatment with ADT.

In the CHAARTED trial, half were randomly treated with ADT, and docetaxel every 3 weeks for six cycles, with the other half on ADT only. The participants had a median age of 63 years. The median overall survival was 13.6 months longer with the ADT/docetaxel combination, at 57.6 months vs 44.0 months on ADT alone. The median time to disease progression was increased to 20.7 months in the combined therapy group versus 14.7 months in the ADT only group.

The upfront addition of docetaxel to ADT also significantly improved every other secondary end-point of relevance to patients. For example, combination therapy doubled the proportion of patients with undetectable PSA, which is a powerful predictor of long-term survival. Additionally, undetectable PSA was maintained at 12 months twice as often in the docetaxel plus ADT group compared with the ADT-only group.

Unfortunately, as with all chemotherapy treatments, a number of unpleasant side effects were reported. One issue: compared with men in a castration-resistant state, men with hormone-sensitive prostate cancer are associated with significant increases in docetaxel absorption and the resultant risk of neutropenic fever. Thus, it’s important never to start docetaxel before patients are treated with 1 to 3 months of hormonal therapy before starting docetaxel. Peripheral neuropathy (usually manifests as numbness or weakness in the fingers or toes) is another risk of chemotherapy, which is potentially irreversible. Other docetaxel reversible side effects include diarrhea (32%), hair loss (65%), loss of appetite (20%), shortness of breath (15%), fluid retention (15%), anaemia (5%) and reduced heart function (10). Most of these are mild and treatable.

Researchers have also studied chemotherapy in non-metastatic prostate cancer.

In the Radiation Therapy Oncology Group 0521 trial, patients with high-risk (Gleason score >7), localized, potentially curable prostate cancer, were randomly assigned to receive ADT for 24 months plus external beam radiotherapy for 8 weeks, with or without six 21-day cycles of docetaxel plus prednisone beginning 28 days after radiotherapy. At 6 years of follow-up, the rate of disease-free survival was 65% in the docetaxel arm and 55% in the non-docetaxel arm. Docetaxel also appeared to improve metastasis-free survival and 4-year overall survival (93% vs. 89%).

The success of the combination treatment excited the urology profession to the extent that the AUA guidelines were amended in 2015 to include this treatment regime. The guidelines for CRPC were again amended in 2018. They are worth reviewing as they identify six indexed patients and offer ‘approved’ therapies for each indexed patient. Refer to Appendix 3 to access these guidelines. The NCCN guidelines have already been upgraded to suggest this joint ADT and chemo approach in all cases where chemo is considered an appropriate treatment. An added benefit is that docetaxel being a generic drug (off patent), is a very affordable drug, unlike many of the new chemo drugs which are very expensive.

Chemotherapy in the Enzalutamide, Abiraterone and Apalutamide Age

Do we start with chemotherapy, or with non-chemotherapy? That is a question that medical professionals need to ask, since the arrival of the above drugs for prostate cancer treatment. The Phase 3 FIRSTANA study helped answer this question by testing docetaxel’s effects in a truly first-line setting. In the worldwide study, 1,168 patients with chemotherapy-naïve mCRPC were randomly assigned to one of three regimens: cabazitaxel 20 mg/m², cabazitaxel 25 mg/m², docetaxel 75 mg/m² with daily prednisone. Median overall survival was almost identical averaging about 24 months. In contrast, in the randomized phase 3 COU-302 trial of men with chemotherapy-naïve mCRPC, starting with abiraterone plus prednisone and then proceeding to chemotherapy after progression led to a median overall survival of about 34.5-month (compared with 30.3 months in the placebo plus prednisone arm).

Progression-free survival in the Firstana trial, median PFS was 5.3 months with docetaxel, which was similar to results in the cabazitaxel 20 mg/m² (4.4 months) and cabazitaxel 25 mg/m² (5.1 months) arms. In the COU-302 trial, median time to radiographic progression was 16.5 months among patients who received abiraterone with prednisone. In a separate trial of enzalutamide-treated patients with chemotherapy-naïve mCRPC, the median time to progression was 18 months. In Firstana, PSA response rates were 68% in the docetaxel group, 69% in the cabazitaxel 25 mg/m² group and 61% in the lower strength group -"the best results we had ever seen in a first-line setting" said Fred Saad, MD, FRCS, University of Montreal Hospital Centre.

From the above results, abiraterone and enzalutamide appear to be at least as effective as docetaxel in treating mCRPC. However, chemotherapy toxicities can be serious, but are manageable given appropriate experience, protocols and procedures. Dr Saad confirmed that in certain circumstances, chemotherapy remains appropriate for some patients with metastatic non-castrate-resistant prostate cancer (mHSPC), and upfront chemotherapy should be considered for some patients with mCRPC and almost all patients with mHSPC.

Men who have a low PSA, but a high burden of mPC lack an androgen receptor therefore pose a much higher risk of treatment failure on ADT. Additional considerations for upfront chemotherapy include high burden of visceral metastases, rapidly progressive moderate to severe symptoms, minimal response to primary ADT, or androgen receptor splice variant-7 (AR-V7) in circulating tumour cells, which predicts worse outcomes in mCRPC. Dr Saad estimated that together, these groups comprise about 10% to 20% of patients who walk through their doors.

Radium-223 (Brand Name: Xofigo®) Manufacturer: Bayer HealthCare

A radiopharmaceutical that is relatively new to the market is radium-223 (Xofigo®) which is mainly used in bone mCRPC. It is also identified by its chemical name: radium Ra-223 dichloride. Xofigo had also shown a delay in metastasis in a number of successful Phase 3 trials. Therefore, this drug can specifically help patients that have CRPC and develop bone metastases (around 90% of patients show some evidence of bone metastases) and who are without known visceral lesions (tumours) elsewhere (external of the prostate).

"Bone metastases can lead to an increase in frequency of skeletal events and are shown to be the main cause of morbidity and death in patients with CRPC," Bayer said.

Bone metastases often results in bone pain, bone fractures, or spinal cord compression that requires treatment. Radium-223 is selectively accumulated in the bone by virtue of its similarity to calcium, (specifically in areas of high bone turnover), by forming complexes with the mineral hydroxyapatite (a main constituent of the bone). The alpha radiation generated during the radioactive decay of radium-223 produces a palliative anti-tumour effect on the bone metastases. Xofigo is administered by intravenous injection with typically six treatments repeated at four-weekly intervals. The short range of alpha radiation of about 2 to 10 cells ensures little damage to healthy tissue, with the radiation not taken up by the bone being cleared, primarily via the gut, and excreted.

The most common side effects reported during the clinical trials were nausea, diarrhea, vomiting and swelling of the legs, ankles or feet. The most common blood abnormalities included anaemia, lymphocytopenia, leukopenia, thrombocytopenia and neutropenia.

The ERA-223 Phase 3 trial found that all grades of bone fractures were significantly higher in men who received abiraterone/prednisone + Figo versus patients who received abiraterone/prednisone + placebo (26% versus 10%). The trial highlighted the significant benefits provided by taking the bone health agents such as bisphosphonates and denosumab. Taking these bone health agents did NOT fully eliminate patients experiencing osteoporosis and other fractures.

Alkaline Phosphatase and Bone Metastases

In men with mCRPC which has spread to the bones, it is important to regularly check their alkaline phosphatase (ALP) in blood levels. ALP is an enzyme which indicates the degree of activity of bone formation and destruction. A high ALP value tells us that bone is being destroyed (and being simultaneously formed) at a greater rate by high osteoblastic activity.

In a healthy person, there is always some degree of bone wear and tear, but the serum ALP level should be below 117 IU/L. If the liver enzymes viz. ALT, AST and bilirubin are in the normal range, this indirectly suggests that the higher ALP levels are mainly coming from the bone. In case of doubt, the lab can provide both bone ALP and liver ALP numbers. (the ‘bone specific’ alkaline phosphatase is referred to as bALP, which is proportional to the enzyme production from osteoblasts. bALP constitutes 40-50% of the total alkaline phosphatase). If the serum calcium is also high then, it suggests that bone destruction is happening more than what is normal wear and tear. The doctor is likely to review the ALP, liver enzyme and serum calcium numbers as a group in order to make a correct judgement about the bone activity. One needs to worry only when there is ALP number trending up or going higher than about 117. The doctor is likely to repeat the blood chemistry tests to determine the trend every few weeks.

A recent research discovery found the ‘crosstalk’ between marrow osteoblasts and cancer cells awakens genes in malignant prostate cells to promote expression of ALP in the cancer cells contributing to the total serum level. This phenomenon is called osteomimicry. This was determined by finding that circulating prostate cancer cells secrete ALP.

Guise T, et al., Future Oncology, 2018, postulated that an elevated “baseline ALP is prognostic for adverse overall survival and may be a better marker for overall survival than PSA in patients with bone-dominant mCRPC.”

With Abiraterone Acetate/Prednisone (Zytiga®): Zytiga is unlikely to directly decrease ALP levels when used to treat mCRPC patients. An indirect effect will likely occur as the tumour burden decreases and bone healing occurs. Clinical experience has shown that ALP levels may ‘flare’ initially after starting Zytiga (e.g., first 2-6 weeks) and later decrease in men who respond to therapy. The initial increase is probably attributable to healing bone and is often noted in patients with a sharp decline in PSA levels.

With Enzalutamide (Xtandi®): Enzalutamide performs exactly as Zytiga as regards ALP levels. Over time as bone remodeling diminishes as a consequence of anti-tumour activity, the ALP levels will decrease.

With Docetaxel (Taxotere®): Docetaxel effects on ALP are indirect, with changes in the tumour causing alterations in ALP levels via the micro-environmental changes that occur as a function of anti-tumour effects. ALP ‘flares’ are less likely with docetaxel.

With Cabazitaxel (Jevtana®): As with docetaxel, cabazitaxel's mechanism-of-action suggests an indirect effect on ALP levels.

With Radium-223 dichloride (Xofigo®): The radium-223 mechanism of action reduces bone formation, directly decreasing ALP levels during treatment. Clinical experience has shown that ALP levels decrease rapidly and usually without any ‘flare’ after initiation of radium-223 treatment, but increase again after completion of the therapy.

Platinum-based Chemotherapy

The global extent of prostate cancer research is massive. Great strides are being made in understanding prostate cancer biology and resistance mechanisms. The therapeutic options for men with CRPC continue to grow steadily. Platinum-based therapies might be the next ‘cab-off-the-rank’, particularly for sub-sets of prostate cancer. Present mainstream ‘drug’ therapies are:

Cytotoxic chemotherapies like docetaxel (Taxotere) and cabazitaxel (Jevtana).

Androgen receptor pathway directed therapies like abiraterone (Zytiga), enzalutamide (Xtandi), and apalutamide (Erleada).

Radium-223 bone - targeted therapy (Xofigo).

An active cellular immunotherapy called sipuleucel-T (Provenge).

In clinical practice all of the above ‘drugs’ have yielded significant short-term benefits. However, their progress has been relatively short - lived and the survival benefits are modest. There remains a pressing need for additional treatment options. Many clinical trials are yielding better results by combining two or more of the above or other treatments (e.g. radiation).

Of the three platinum drugs that have been available for some years, cisplatin and oxaliplatin use is often limited by renal impairment and neuropathic (nerve) toxicity. Carboplatin is generally well-tolerated, but has a challenging footprint in terms of myelosuppressive effects. These effects include the decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes) and bone marrow suppression.

Satraplatin, a fourth-generation oral platinum therapy, was tested in the randomized SPARC phase 3 study. This large study failed as it offered no overall survival benefit, but did record significant PSA reductions. The results suggest that the compound may offer efficacy to sub-sets of prostate cancer patients. Another mCRPC trial suggested a 33% reduction in disease progression or death versus placebo and a significant reduction in pain experienced.

Platinum compounds are successfully used in treating small cell lung cancer. It is thought that they will also be successful in treating the extremely rare small cell carcinoma prostate cancer (SCCPC). The results of limited prostate cancer studies have led to the uptake of platinum compounds to treat SCCPC. It is worth noting that this treatment is not incorporated in any national professional practice guidelines.

A further series of trials with carboplatin plus docetaxel plus estramustine phosphate have reported > 50% reduction in PSA in 63% to 95% of HSPC patients all with acceptable toxicity. A small study with carboplatin saw six or eight men have a PSA reduction of > 50% in 12 weeks in BRAC2 compromised men

Treatment of mCRPC with a combination of cabazitaxel and carboplatin showed improved clinical efficacy compared with cabazitaxel alone, according to the findings of a Phase 2 trial in 160 mCRPC men. The investigators from the University of Texas MD Anderson Cancer Centre in Houston, stated that, to their knowledge, the randomized trial is the first to establish the benefit of combining a platinum agent with a taxane agent. At a median follow-up of 31 months, the combination arm had significantly longer median progression-free survival compared with the monotherapy arm (7.3 vs 4.5 months). Patients who received the dual regimen had a significant 31% decreased risk of progression compared with those in the cabazitaxel-only recipients. These results were reported in the September 19 online Lancet Oncology.

Neuroendocrine prostate cancer which develops (fortunately in very few men) as an adaptive response to long-term exposure to ADT and AR blockade, is generally considered to be responsive to platinum therapies. The response rates are as high as 70% in those with poorly differentiated histology. A challenging, but definitive molecular characterization is needed to recognize the subgroup who may be good candidates for platinum therapy.

Recent research suggests that prostate cancers that have deficiencies in the DNA damage repair pathway are also associated with a higher likelihood of response to platinum agents (and PARP inhibitors). Platinum compounds exert their anti-neoplastic activity (stopping abnormal and excessive growth), which result in double-stranded DNA breaks. Loss-of-function mutations or alterations to genes BRCA1, BRCA2, ATM, CHEK2, PALB2, and RAD51D, etc., all of which are important in the repair process for double-stranded DNA breaks, make it more difficult for the disease to withstand the effects of platinum therapy.

Carboplatin and paclitaxel (CP) offered moderate efficacy in treating CRPC in 58 men with most men having homology-directed repair gene defects, in a retrospective review. Twenty-seven patients received CP as the first-line chemotherapy, 21 as the second-line after docetaxel, and 10 as the third-line after docetaxel and cabazitaxel. PSA responses at any time were 55.6%, 19.0%, and 10.0%; the median progression-free survival was 3, 1, and 1 month; and the median overall survival was 19, 11, and 6 months, respectively, for the first-, second-, and third-line settings. CP worked best in the first-line setting, but shows little effect in the third-line setting. CP after docetaxel and cabazitaxel may be recommended in selected patients with CRPC with homology-directed repair gene defects. One CP shows moderate efficacy against CRPC in the first-line setting, but shows little effect in the third-line setting. CP after docetaxel and cabazitaxel may be recommended in selected patients with CRPC with homology-directed repair gene defects. One third-line setting patient with a deleterious germline BRAC2 mutation, had an exceptional and durable PSA response. Minimal adverse events were evident in all settings.

Next-generation sequencing of circulating tumour cells or cell-free DNA analysis are already in limited use to identify patients most likely to benefit from a platinum-based treatment. PARP inhibitors in their action have some complementarity to platinum agents. It is felt that the use of these different agents might yield better results due to their different resistance mechanisms.

The treatment of patients with metastatic cancer is a complex business. The pros and cons are best left to an oncologist to explain as each patient will display unique characteristics that need to be considered when structuring a treatment regimen.

The recent changes in therapeutic treatments for patients with mCRPC have questioned the detection methods being used for metastatic cancer. Oliver Sartor, et al., in their paper “Unmet Needs in the Prediction and Detection of Metastases in Prostate Cancer” raised some interesting questions about the drugs used for the treatment and the improved detection of metastatic prostate cancer.[3] An important study was reported on at the 2014 ASCO meeting in Chicago. The study compared androgen deprivation therapy (ADT) alone vs ADT plus docetaxel chemotherapy in men with newly diagnosed metastatic prostate cancer. The study found that overall survival was improved by about 14 months, in the combination-therapy group. With regard to the high-risk patients (those who had either four bone lesions or visceral metastases), the overall improvement in survival was 17 months. There was also a delay in time to castrate-resistant disease.[4]

Cancer related fatigue (CRF) is a common and debilitating symptom that can influence quality of life in cancer patients. Reported interviews with advanced cancer patients, highlight CRF's profound impact on the patients' lives. Themes that dominated the interviews included: ‘dependency on others,’ ‘loss of power over decision making,’ and ‘daily living disruption.’

One final word on chemotherapy. There have been a number of reported instances where groups of oncologists were asked whether or not they would take or give to their family members, the chemo that they were prescribing for their patients. Interestingly, the spread of responses suggested that between two-thirds and three-quarters would not do so.

Immunotherapy

Immunotherapy is a new class of cancer-fighting tools that rely on stimulation of the immune system of the body to enable them to destroy cancer cells. An excellent pictorial illustration of the path to successful immunotherapy discovery and treatment is accessible via Appendix 3. When prostate cancer continues to grow, despite the lowering of testosterone levels by hormone therapy, treatment options become more limited. Sipuleucel -T or secondary hormone therapies such as abiraterone, enzalutamide or apalutamide may be added to the therapy regime, and are followed by chemotherapy agents, docetaxel or cabazitaxel. Access more information via Appendix 3.

Many early immune-based treatment protocols have only produced mediocre results. It is becoming clear that in the cell micro-environment, that multiple therapies are likely to yield the best results. This factor has led to the establishment of a number of clinics in Germany, Mexico and even the USA, that treat cancer patients with a number of immune-based protocols concurrently, to yield the best outcomes.

Many prostate cancer sufferers see their cancer progress to the hormone-refractory or castration-resistant stage, which seriously limits standard medical treatments. This is where immunotherapies come to the fore.

Dr Ralph Steinman was awarded the Nobel Prize in Medicine 2011 for his discovery of the dendritic cell and its role in adaptive immunity. Dr Harmon Eyre, at the American Medical Association commented at the time about dendritic cells: “Patients’ responses are far out of proportion to anything that any current therapy could do.”

What are dendritic cells and what do they do? They are highly specialized antigen-presenting immune cells that play a key role in the immunological reactions throughout the human body. They are responsible for identifying pathogens such as viruses, bacteria, fungi, and malignant cells, by presenting their identifying markers (antigens) to specific T-lymphocytes. These T-lymphocytes then multiply and attack the diseased cells, whilst ignoring normal healthy cells.

In 2010 the FDA approved the use of dendritic cell vaccine treatment in the USA. A significant number of clinical trials have confirmed the efficacy of this form of treatment.

Sipuleucel-T (Provenge®) was the first therapeutic cellular immunotherapy to demonstrate effectiveness in Phase 3 clinical trials by prolonging the life of patients who have advanced to the late stage of the disease with mCRPC (which is sometimes called asymptomatic, Hormone-Refractory Prostate Cancer (HRPC). It is specifically prepared using harvested dendritic cells from the patient’s white blood cells, which are incubated with a two-part fusion protein. The resultant blood product is returned to the infusion centre for re-infusion into the patient. This re-infusion leads to an immune response against cancer cells carrying the PAP antigen. This very expensive treatment, outlined by Philip W. Kantoff, et al. after a Phase 3 clinical trial, was shown to prolong life with a 4.1-

month improvement in median survival (25.8 months in the sipuleucel-T group verses 21.7 months in the placebo group.[2]

A number of clinical trials are now at Phase 2 level which are studying sipuleucel-T for use with a second compound. Access more information via Appendix 3.

Another promising immunotherapeutical agent is PROSTVAC®, which is a therapeutic vaccine being developed by Bavarian Nordic A/S. It has moved to a large phase 3 clinical trial, after a randomized phase 2 trial involving 125 patients with metastatic CRPC, showed an 8.5 month improvement in median overall survival.[5] The PROSPECT Phase 3 trial recruited 1298 patients in 15 countries and compared the vaccine by itself and in combination with the GM-CSF growth factor versus a placebo. The trial was aborted in 2018, when the interim results failed to confirm the overall survival benefit achieved in the Phase 2 trial. Such is the price of progress: expensive and slow. All is not lost with PROSTVAC, as additional clinical trials are underway to evaluate the potential clinical benefit of combining PROSTVAC with different treatment modalities such as hormonal therapies (e.g. androgen inhibitors), radiopharmaceuticals and immune checkpoint inhibitors in the treatment of prostate cancer.

In 2016, the US National Cancer Institute lists 22 clinical trials that were underway using cancer vaccines. Most of these trials involve the vaccine being used in combination with another treatment that has already been approved. It is being found that this dual attack on the cancer is yielding better results than by use of a monotherapy alone. The National Cancer Institute have an excellent summary of cancer vaccine developments on their web site accessible via Appendix 3.

Numerous institutions and biotechnology companies world-wide are spending vast amounts of money to develop immuno-therapeutical treatments that promise to radically change the prostate cancer treatment landscape in coming years. One of these (Memorial Sloan Kettering Hospital) is concluding a Phase 1 clinical trial that will evaluate the safety and effectiveness of different doses of a patient’s own immune cells (T cells). These T cells have been changed to help recognize and destroy the patient’s prostate cancer cells by targeting a protein called prostate-specific membrane antigen. It is hoped that this approach will help each patient’s own T cells recognize his prostate cancer cells and possibly kill them.

Over recent years, an array of immunotherapeuticals have been very successful in treating cancers of the lung, kidney, head and neck and even advanced melanoma. Sadly, the efficacy of these single agents such as cytotoxic T-lymphocyte-associated antigen 4 antagonists (CTLA-4), programd cell death 1 (PD-1), and PD-ligand (PD-L1) have been limited to very few prostate cancer patients. The combination of these agents together with small-molecule inhibitors, vaccines or immune-modulating agents, in various clinical trials, is offering variable progress. These agents offer different mechanisms of action and have entirely new structures.

Most immunotherapeutic research is broadly split into two broad categories: firstly, treatments to stimulate or boost immune effector functions including cytokines, vaccines, oncolytic viruses, adoptive cell transfers and adjuvants. Secondly, to use counter immune-suppressive mechanisms (immune checkpoints and immune modulators). Some of these will be exposed in Chapters 15 and 16, after we have exposed readers to a little more technical insight into the biology involved.

Caris Life Sciences®, leaders in precision medicine profiling field, have another interesting technology called the Carisome® Microvesicle Technology. This blood-based highly-reproducible technology platform has the ability to identify and characterize circulating microvesicles (cMV’s) released in the blood that serve as a signalling device for various types of cancer. cMV’s are sub-cellular membrane-bound vesicles, ranging from 30 to 1500 nm in size, that can be found circulating in the blood and other body fluids. They are released from various cell types, under both normal and pathological conditions, which include cancer. The key attribute of the cMV's is that each population of cMV's expresses an array of proteins that reflects its cell-of-origin. The cMV's contain a 'cargo' of their cell of origin, proteins and RNA, which should provide information similar to that which would be obtained from a direct tissue biopsy. Hopefully, when this research is successfully concluded after clinical trials in the future, it is likely that a 'liquid biopsy' will be possible, meaning patients may be able to avoid needle biopsies.

This technology is not specifically focussed on prostate cancer, but on cancer generally. It is included to illustrate the very rapid progress that is being made in proteomics (the science of proteins) and other biomarkers.

A recent research paper by I. Giusti, et al., highlights the potential use of vesicles as prostate cancer biomarkers.[7]

We are seeing a number of companies introduce circulating tumour tests for metastatic cancer patients for the prostate, breast and ovarian cancer. The results of these tests dictate which therapies are likely to be most successful. In 2016, Foundation Medicine Inc., introduced their circulating tumour cell test for prostate cancer. Their FoundationOne Liquid blood-based assay provides targeted gene and microsatellite instability (MSI) results that can help direct therapy selection and clinical trial options for advanced-stage cancer patients. More on MSI in Chapter 15.

Re-purposing of Older Drugs

When older drugs come off patent and become generic, big pharma quickly lose interest in them, as their profit margins are squeezed and they have their 'great new drug’ to bring to market. This leads to perfectly effective drugs slowly, but surely, disappearing from the doctor’s prescription pad.

Then there is the question of older drugs that have been developed and used to combat a specific condition, where subsequent research has shown the drug to have efficacy in fighting cancer. This leads me to what I consider to be a most important book on cancer. The book “How to Starve Cancer” was written by Jane McLelland, an English physiotherapist, who in 1994 was stricken with cervical cancer and give only a few months to live. It is pleasing to report that 25 years later, she is alive and well having survived lung cancer and leukemia. How did she manage to achieve what she has. In brief, she identified a series of older drugs and supplements, that together attacked signalling pathways that promoted her cancer. Even after her initial cancer was controlled, she continued her research into anti-cancer substances and even accelerated her research after the further two cancer types struck her.

In her book, she tells of accompanying a girl friend of hers, together with the girl friend’s two adult sons, to see an oncologist about the friend’s advanced triple-negative breast cancer. She showed the oncologist the list of drugs and supplements and supporting science, that she had used to cure herself. Not surprisingly, the oncologist threw her out of his rooms, and demanded the friend follow his treatment protocol exactly. The two sons physically attacked Jane and called her a ‘quack’. About 6 months later the friend died, but the story doesn’t end there. Some 4 years later the oncologist opened a London cancer clinic to treat advanced cancer patient using Jane’s protocol! This clinic continues this therapy to this day, with Jane acting in a consultative capacity to the clinic.

In the book, she outlines a MetroMap that details her therapy for various cancers. Recently, the MetroMap V2.0 has appeared that details a protocol to fight prostate cancer. It is accessible via my web site at http://www.anabcofprostatecancer.com.au. Listed below are a partial list of these drugs, but first a warning: If you are considering the use of any of the drugs that follow, it is essential that they be taken under the supervision and direction of a

Board-registered doctor who has been fully-trained in integrative medicine. It is why I have included minimal information describing each drug. (for supplements used in MetroMap V2.0, see Chapter 20).

Metformin:

Original Use: A drug to treat Type 2 diabetes

New Use: Kills cells that lack PTEN or p53 genes. Promotes glutamine metabolism. An autophagy inhibitor.

Niclosamide:

Old use: An anti-tapeworm medication.

New use: Inhibits AR variants expression and may overcome enzalutamide resistance in mCRPC.

Dipyridamole:

Old use: A medication that inhibits blood clot formation when given chronically and causes blood vessel dilation.

New use: Usually part of a multi-cocktail that may reduce tumour growth and metastasis.

DIM: (Diindolylmethane).

Old use: Used to treat recurrent respiratory papillomatosis.

New use: Promotes gamma estrogen receptors which suppress cell proliferation.

Doxycycline:

Old use: An antibiotic used in the treatment of infections caused by bacteria and certain parasites.

New use: Scientists at the University of Salford have shown that cancer stem cells can be defeated by a 'double punch' of doxycycline in combination with vitamin C.[37]

Itraconazole:

Old use: An antifungal medication used to treat a number of fungal infections.

New use: It has potent anti-angiogenic activity and can inhibit the Hedgehog signalling pathway.

Naltrexone: Low dose (LDN) only.

Old use: A medication primarily used to manage alcohol or opioid dependence.

New use: LDN act directly to stimulate immune receptors called Toll-like receptors. These can produce inflammatory compounds that stimulate cancer cells. LDN blocks this and also cancer cell division. Additionally, it is an anti-inflammatory, it modifies certain genes and promotes cancer cell death, it provides pain relief, and it blocks Opioid Growth Factor, which is present in about 90% of all cancers.

Mebendazole:

Old use: Used to treat a number of parasitic worm infestations.

New use: It has potent anti-angiogenic activity and can inhibit the Hedgehog signalling pathway.

Hydroxychloroquine:

Old use: A medication used to treat malaria.

New use: It can decrease tumour growth by cutting off the fuels that promote mitochondrial function. There are multiple Phase 1 and 2 trials testing the efficacy of hydroxychloroquine.

There are numerous other re-purposed drugs like aspirin, cimetidine, dexamethasone, melatonin, statins and digoxin that are receiving attention as anti-prostate cancer agents. All these, except digoxin, are included in the MetroMap V2.0.

Summary – Chemotherapy and Immunotherapy

Patients diagnosed with T3 or T4 prostate cancer (after a positive biopsy and positive bone scan, PET/CT scan and/or MRI scan) are likely to be referred to an oncologist with chemotherapy to be part of the treatment regime. If the cancer is found in the bone, bisphosphonate treatment might be recommended. Bisphosphonates inhibit a type of bone cell that breaks down bone and reduce the pain of bone cancer. Chemotherapy is often prescribed if hormone therapy becomes ineffective. This situation generally occurs when the cancer cells no longer need testosterone to grow.

A frequent initial chemo drug of choice is docetaxel usually given with the steroid drug prednisone. If this drug does not work (or becomes ineffective), a newer drug called cabazitaxel often heads the list of the next chemo drug to be tried. Newer drugs with fewer side effects continue to become available. One is radium-223 (Xofigo®) which is mainly used in bone mCRPC.

Immunotherapy is providing a new class of cancer-fighting tools that rely on stimulation of the immune system of the body to enable them to destroy cancer cells. One such agent is PROSTVAC®, which is a vaccine that has moved to a Phase 3 clinical trial after the Phase 2 trial showed 8.5-month improvement in median overall survival in metastatic CRPC patients.

Sipuleucel-T is the first and to date the only therapeutic cellular immunotherapy approved for use by the FDA for the prolonging of the life of patients who have advanced to the mCRPC stage of prostate cancer. Virotherapy (a therapy using viruses) looked to be a promising tool for treating various cancers, but its use in prostate cancer therapy has been disappointing.

Some Factors in favour of Chemotherapy and/or Immunotherapy

Chemotherapy is an important component in the treatment of patients with metastatic cancer.

Newer drugs are extending overall survival periods in metastatic CRPC patients with fewer serious side effects being experienced.

Immunotherapy will become a very important tool in fighting metastatic cancer in future years.

Some factors against Chemotherapy and/or Immunotherapy

Even the newer drugs have unpleasant side effects.

Prostate Cancer Therapy Options

Therapy	Mechanisms	Examples
Anti-androgens	**All:** Bind to the AR and block activation of the AR. **Xtandi®, Erleada™:** Prevent translocation of the AR to the nucleus and inhibit interaction with DNA	**Taken Orally:** Casodex® (bicalutamide) Eulexin® (flutamide) Nilandron® (nilutamide) Xtandi® (enzalutamide) Erleada (apalutamide)
Luteinizing hormone-releasing hormone (LHRH) agonists	Overstimulate the pituitary gland to downregulate the GnRH receptor, decrease LH production, which lowers testosterone production in the testes	**Subcutaneously:** Eligard®(leuprolide acetate for injectable suspension) **Intramuscular:** Lupron Depot® (leuprolide acetate for depot suspension) Trelstar® (triptorelin pamoate) **Subcutaneous Implant:** Zoladex® (goserelin acetate) Vantas® (histrelin acetate)
Luteinizing hormone-releasing hormone (LHRH) antagonists	Block GnRH receptor, decrease LH production, which lowers testes testosterone production.	**Subcutaneously:** Firmagon® (degarelix)

Prostate Cancer Therapy Options (Continued)

Therapy	**Mechanisms**	**Examples**
Androgen biosynthesis inhibitors	Inhibits biosynthesis of testosterone by blocking an enzyme that is needed to produce a testosterone precursor.	**Taken Orally:** Zytiga®(abiraterone acetate)
Immunotherapy	Enhance the ability of the patient's immune system to attack cancer cells.	**Taken by IV Infusion:** Provenge®(sipuleucel-T)
Radiation therapy	Use of charged particles or waves directed towards cancer cells to induce tumour cell death.	**Taken by IV Infusion:** Xofigo® (radium Ra ^{223} dichloride)
Chemotherapy	Damage DNA and inhibit cellular machinery involved in cell division to impair mitosis of malignant cells.	**Taken by IV Infusion:** Taxotere® (docetaxel) Jevtana® (cabazitaxel)
Bilateral orchiectomy	Surgically remove both testes to reduce testosterone levels.	

Image: Our 5-star luxury apartment complex some 20 km from the NCC.

Chapter 15.

Metastatic Prostate Cancer, Diagnosis, Genetics and Precision Medicine

In this chapter, I focus on metastatic cancer. That is prostate cancer that can kill. Prior to the start of this century, most men with metastatic cancer had few chances of surviving once their cancer had become metastatic and castration-resistant. Chemotherapy was the primary tool available to the oncologist. Men had to endure the severe side effects that chemo drugs imposed on patients. Many men were unable to complete their chemo regimes due to the severity of these overwhelming side effects. Others persevered only to find that the disease progressed, perhaps after being held in check by the chemo for some time.

As an aside, when I wrote the two earlier editions of this book, I felt it inappropriate for me to address Stage 4 metastatic castration-resistant prostate cancer in any detail, due to the seriousness of the condition and the need for such patients to focus on the best medical advice available from medical specialists. As a regular speaker at prostate support groups in Australia, I have come across many men, who seemed to me, to be without hope. They lacked confidence that they would survive the disease and they awaited what was likely to be a challenging death from prostate cancer. My own brother was told by an oncologist: “You only have two years to live; eighteen months in reasonable comfort, followed by six months of hell.” A disgusting comment, particularly considering that my brother was still in reasonable health, three years later. (Sadly, on the 22nd January 2020, he lost his battle with cancer after the same oncology team denied him access to the experimental drug Veyonda which might have prolonged his life).

I know that my skill set allows me to extensively interrogate the research and clinical literature and present better options that patients can discuss with their medical team.

Medical professionals are not infallible. They make mistakes, some more often than we might expect. Just today, Recently, I became aware of the following error by a pathologist examining a prostate biopsy: Last month, a man called the editor of Bob of the Balloon[1] and said he'd been diagnosed with prostate cancer. His local pathology lab rated his Gleason score at 9 (5 + 4). The editor asked if he'd gotten a second lab to read his slides. He hadn't. So he sent his slides to one of the premier U. S. pathologists, Dr. David B. The results came back Gleason 7 (3 + 4). Wow! That's a significant difference, and the treatment protocol would be reflective of that difference. This example, again, highlights the importance of obtaining a second—and sometimes third—opinion, particularly with pathology results.

Metastatic Cancer

There are three forms of metastatic prostate cancer. Firstly, prostate cancer that is external of the prostate gland, but is still responsive to androgen drug therapy. In short, metastatic hormone-sensitive prostate cancer (mHSPC). In the absence of successful treatment, it is likely over time (months or years) to advance to mCRPC.

Secondly, prostate cancer that is external of the prostate gland, but is no longer responsive to androgen drug therapy. In short, metastatic castration-resistant prostate cancer (mCRPC).

Thirdly, there is a deadly treatment-resistant prostate cancer sub-type called neuroendocrine prostate cancer (NEPC). No effective treatment for NEPC exists. The development of a variety of effective anti-androgen therapies for prostate cancer has been a fantastic scientific advance. However, some men who receive these targeted treatments are more likely to develop NEPC. Fortunately, NEPC only develops in very few men, but in an era of more biopsies, its prevalence is likely to be understated.

"NEPC is essentially a new cancer. From what it 'eats' to how it looks, the tumour cells are completely re-programd. The tumour even loses the receptor that is targeted by current treatments, which is why it is so difficult to treat," said Jorge Moscat, Ph.D., a study author and director and professor in SBP's Cancer Metabolism and Signalling Networks Program. "Identifying the switch that drives the transformation from prostate cancer to NEPC is a critical first step toward developing treatments that prevent treatment-resistance in men with prostate cancer before it begins."

This scientific team identified epigenetic patterns -- molecular tags that modify DNA -- associated with NEPC, linked to the expression of an enzyme, phosphoglycerate dehydrogenase (PHGDH), which could be a treatment target for NEPC. The team are trying to identify a drug that can block PHGDH. They have already found a FDA-approved drug that inhibits epigenetic changes, called decitabine, which holds promise as a future treatment for NEPC.

Neuroendocrine prostatic carcinomas are often diagnosed on primary prostate needle biopsy or on biopsies of metastatic lesions. A characteristic of NEPC is negligible or low PSA levels. Which is probably why about 50% of NEPC patients present with mCRPC and have a median survival of 9.8 to 13.1 months. A further challenge facing oncologists is the variability of cell phenotypes in NEPC cases: small cell neuroendocrine carcinoma - a rare high-grade epithelial neoplasm of the prostate (about 0.35 cases per million per year); large cell neuroendocrine carcinoma and carcinoid tumours, which are the least aggressive form.

Let’s look at metastatic cancer more fully:

The earliest stages of metastases are microscopic and therefore invisible even with today's imaging technology. To be detected with the best available PET scan technology, small tumours must measure more than 3mm (1/8") diameter. For detection with standard CT scans and MRI scans, the tumour must be greater than about 12mm (1/2") in size.

Cancer that spreads outside the prostate gland is what makes prostate cancer dangerous. Over time, the metastatic prostate cancer cells cause malfunction by impeding normal function. Lymph nodes, particularly in the pelvic area, are often an early site for metastases to occur. Fortunately, lymph nodes continue to function effectively, even if the cancer spread is extensive. Therefore, it is the least dangerous form of prostate cancer metastases. At the other end of the spectrum is the liver, which is far less tolerant. Liver metastases, therefore, usually represents a very serious and life-threatening condition. It generally occurs after the patient has undergone and failed other therapies and once it occurs it progresses rapidly. Liver metastases may be present when standard blood tests (ALT, ALP and ALT) register outside the normal range. Blood test anomalies are generally followed up by a PET scan, CAT scan or MRI of the abdomen and pelvic area. Hormone therapy with Lupron (or similar), abiraterone acetate (Zytiga), enzalutamide (Xtandi), or chemotherapy (Taxotere), Jevtana and Carboplatin, are generally the standard approach to treat liver metastasis. However, it is likely that one or more of these treatments may have already been tried or may no longer be effective. More recently, radioactive microspheres injected directly into the tumour, called SIR-Spheres, have shown notable efficacy with very tolerable side effects.

The seriousness of bone metastases, the most common site of prostate cancer spread, lies about half way between that of node metastases and liver metastases. It should be noted that there are many types of prostate cancer. There is little heterogeneity between tumours and even within a single tumour. There are low-grade 'cancers' which seldom spread; which are genetically distinct and represent a totally different category of disease.

Four factors are considered when looking at metastatic cancer: the site of the tumour/s; the extent of their spread; the tumour cell growth rate and the efficacy of available treatment.

Genetics

Author's Note: This book has been written to be easily understood by the average reader. The balance of this section contains content that is more complex and not as easily understood. Skip sections that are challenging.

The largest study to date on the genetics of prostate cancer has found that 17% of prostate cancer patients have a disease-causing genetic variant associated with more aggressive disease and poorer health outcomes. Previously, that number was thought to be closer to 12%.

Thus, genetics are becoming increasingly important in determining the best treatment regime to be followed by many, but a minority of men. It is no longer acceptable for treatments to be undertaken that do not work due to genetic incompatibility. Much time, money and emotion capital can be saved by using the most effective treatment from the start of therapy.

So, what are genetics and how do they fit into the prostate cancer picture? We learned in Chapter 3 about the two-stranded double helix which is deoxyribonucleic acid (DNA) and that a gene is a unit of DNA usually located on a chromosome. We also learned that cancer is considered to be partially or wholly due to errors in only a relatively small number of genes. Also, that genes and nucleotides are associated with the specific functions of each cell such as cell proliferation or growth, control of cell functions, and ongoing cell behaviour. There are only four types of nucleotides in DNA (Types G, C, T and A). Errors in the coding of a small number of these nucleotides, their absence or duplication, results in ‘rogue’ activity by the affected cells. This rogue activity generally manifests itself in the form of cancer.

There are two types of gene mutations: somatic or germline. The latter are inherited and somatic mutations spontaneously occur years after birth. Somatic mutations can be caused by a variety of factors: internal (errors in cellular replication and oxidative damage) or external (exposure to harmful substances, which damage the DNA of germ cells). Suspected germline mutations and genetic testing are relevant to cancer treatment and prevention. A positive germline test may suggest that other close family members might also carry the same mutations and as such, could benefit from genetic testing. For men with high-risk prostate cancer, the use of genetic testing for inherited germline mutations is becoming standard of care.

A considerable research effort has gone into identifying and characterizing somatic mutations in prostate tumours. A recent paper listed over 100 genes which were mutated (including DNA copy number alterations, fusion genes and point mutations) at significant rates in prostate cancer. This marked the first time an extensive catalogue of mutations in both localized and metastatic prostate cancer became accessible. Excitingly, somatic DNA alterations in BRCA2, AR, TP53, PTEN, CDK12, RB1 and MYC, have been identified as being among the most common and important drivers of metastatic versus indolent disease.

Tumours are heterogenic in make-up and include more than one type of cell, but their initiation and continued growth is usually dependent on a single population of neoplastic (abnormal proliferating) cells. Whilst somatic alterations may occur in cancer cells as a response to internal or external stress, these alterations are modulated by type and degree by the inherited genes.

A clear example of the germline being in ‘charge’ is shown by the microsatellite instability (MSI) resulting from mismatch repair defects (MMR) in cancer cells which have mutations in mismatch repair genes including MLH1, MSH2, MSH6 and PMS2. (MSI and MMR – See details later in this chapter).

Precision Medicine

Comprehensive genomic profiling (CGP) is increasingly used for routine clinical management of prostate cancer. I recently listened to a podcast by one of the most eminent urologists in the USA. He stated that CGP is becoming an important tool in characterizing his patients’ prostate cancer. He compared it increasing use to the very rapid uptake of mpMRI as a prostate cancer diagnostic tool. Over time it will become standard procedure.

In support of this statement, one of the leaders in the field, Caris Life Sciences, have to date, processed on their Caris Molecular Intelligence platform, the following numbers of assays:

PDL1 – Programd Death-Ligand 1 by IHC: 77,000 + tests done.

MTB – Mutational Tumour Burden by NGS: 46,000 + tests done.

MSI – Microsatelite Instability by NGS: 37,000 + tests done.

So far, targeted therapies for prostate cancer have focused on blocking androgen receptors or reducing hormone production. Over time, prostate cancers find ways to circumvent them and the cancer returns, often more aggressive than before.

“We often feel helpless,” said Dr Agarwal (Huntsman Cancer Institute in Salt Lake City, Utah, who is also senior author of the study reported on below). He continued: “Unless we know the drivers of prostate cancer at the cellular and molecular level, we will never be able to go beyond what we are doing right now. As more molecular drivers of prostate cancer become known, more options become available for treating mCRPC. In more than half of the patients (in the paper reported on below), there is a molecular target that is targetable by a drug either currently available in the clinic, or currently available under investigation in a clinical trial.”

Jon H. Chung, PhD et al., in a paper titled, “Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumours.” (JCO Precision Oncology - published online in May 2019) reported the results of 3,476 clinically advanced prostate cancer tumours that were analysed by CGP for genomic alterations (GAs) and signatures of genomic instability.

The prostate cancer samples (1,660 prostate gland and 1,816 metastatic site tumours) were analysed by CGP using the FoundationOne Assay (Foundation Medicine, Cambridge, MA – this assay has now been upgraded to the FoundationOne CDx Assay) for GAs and genomic signatures (genome-wide loss of heterozygosity [gLOH], microsatellite instability [MSI] status, and tumour mutational burden [TMB]). Frequently altered genes were TP53 (44%), PTEN (32%), TMPRSS2-ERG (31%), and AR (23%). Potentially targetable GAs were frequently identified in DNA repair, phosphatidylinositol 3-kinase, and RAS/RAF/MEK pathways. DNA repair pathway GAs included homologous recombination repair (23%), Fanconi anaemia (5%), CDK12 (6%), and mismatch repair (4%) GAs. BRCA1/2, ATR, and FANCA GAs were associated with gLOH-high, whereas CDK12-altered tumours were infrequently gLOH-high. Median TMB was low (2.6 mutations/Mb). A sub-set of cases (3%) had high TMB, of which 71% also had MSI-high.

What does all this gobbledegook mean? It informs the clinician as to what therapies are likely to work or not. Examples:

Genomic alteration gLOH - PARP inhibitors are likely to work.

Signatures of genomic instability - MSI/TMB – immunotherapies are likely to work.

The last few years have seen a huge advance in molecular profiling which presents the clinician with nearly essential information for all men with metastatic solid tumours. This practice has led to the emergence of the terms ‘personalised’ or ‘precision’ medicine. The molecular profiling field is evolving rapidly. More recent practice sees clinicians calling for more broader panel testing rather than testing for just a few genes or gene products. These genomic alterations serve as biomarkers which indicate the likely aggressiveness of tumours and the patient’s likely response to various therapies as well as a possibly entry into a clinical trial. In addition to the detection of relevant biomarkers, the Next Generation Sequencing (NGS) methodology is used to determine the four main classes of genomic alterations (base substitutions, insertions and deletions, copy number alterations and re-arrangements).

The growing incidence of evidence-based biomarker testing has led to many medical insurance companies accepting claims for such testing. One of the more popular molecular profiling assays recently approved by the FDA is the FoundationOne CDx assay (Foundation Medicine). It is a single test that analyses all 17 FDA guideline-recommended genes in solid tumours, including companion diagnostic indications with a direct path to therapy such as tumour aggressiveness and appropriateness of various therapies. Every test result includes microsatellite instability (MSI) and tumour mutational burden (TMB) data to help inform immunotherapy decisions. A PD-L1 immuno-histochemistry (IHC) test is sometimes added to help determine the optimal therapy. The test uses tissue samples obtained via needle biopsy, etc. The assay which surveys 324 genes, cost US insurance companies $3500 in 2019. The MSK-IMPACT assay, which offers analysis of 468 cancer-associated genes is also approved by the FDA, but is apparently not yet covered by Medicare, as it is not considered a companion diagnostic.

Invitae Corporation in August 19 started to offer their 84 Gene Cancer Panel Test at no charge, which also includes free genetic counselling. They are able to do this due to a sponsorship deal. This (and their other genetic tests) offer the following benefits to the patient’s medical team: better risk stratification and surveillance; improved opportunities to get into clinical trials and better treatment decision-making for chemotherapy, and targeted therapies such as PARP inhibitors, and immune checkpoint inhibitors such as pembrolizumab.

For oncologists, the Guardant 360® assay provides comprehensive genomic results in approximately seven days from a simple blood draw. It covers all genes recommended for profiling by the NCCN. In the largest comparison of blood based MSI testing to traditional tissue methods across multiple solid tumour types, researchers demonstrated that the Guardant 360® assay can accurately detect MSI, the important biomarker used to predict response to immunotherapy regardless of tumour type.

Many readers of this book will have done saliva DNA tests to trace their heritage. The Institute of Cancer Research in the UK are trialling with UK general practitioners, a similar, but more accurate ‘spit’ test that will look at up to 150 genes.

There are also several other NGS tests that are approved by the FDA that target a specific gene or several genes.

Microsatellite instability status

Microsatellite instability (MSI) is a form of genomic instability caused by the insertion or deletion of repeating bases, called microsatellites, during DNA replication and the failure of the DNA mismatch repair (MMR) system to correct these errors. MSI status is a measure of MMR deficiency commonly found in solid tumours, providing clinicians and patients better information to determine the best treatment path.

FDA's approval of Merck's checkpoint inhibitor Keytruda® (pembrolizumab) was for patients with solid tumours identified as having high microsatellite instability (MSI) or mismatch repair (MMR)-deficient. The approval was an important first for the cancer community – the first time the agency had approved a drug based on biomarkers of patients' tumours, rather than the location in the body or the tumour type. MSI is determined by a PCR-based assay (Promega Corporation) using biopsy tissues.

Mismatch repair

DNA mismatch repair (MMR) is a bio-mechanism used to restore DNA integrity after the occurrence of mismatching errors, including single base mismatches or short insertions and deletions. Four genes that play a critical role in this process include: MLH1, MSH2, MSH6 and PMS2. The inactivation of one of these genes, which can occur due to germline and/or somatic mutations or to epigenetic silencing, results in a defective MMR (dMMR) mechanism. MMR defects are analysed by an immune-histochemistry assay that determines and quantitates the expression of the above four most common MMR proteins.

The overall response rate in the 149 patients (mostly colon cancer patients) in the Keytruda® (pembrolizumab) trial (that led to FDA approval) was about 40 percent. In 80 percent of those patients who responded at all, the responses lasted for more than six months, once again confirming the outstanding durability of responses to immunotherapy. (Refer to the detailed description of Keytruda® on page 249). The adoption of MSI and MMR testing in clinical practice to identify patients suited to Keytruda® therapy is essential.

PARP inhibitors and platinum-based chemotherapy are also possible therapies in metastatic patients who are carriers of mutations in DNA mismatch repair genes. To put the issue of DNA repair into perspective, the incidence of germline mutations in genes mediating DNA-repair processes among men with mCRPC, in a multi-centre study, was 11.8%, which was significantly higher than the incidence among men with localized prostate cancer (4.5%) and 2.7% in men without prostate cancer.

Tumour mutational burden (TMB)

The total number of mutations (changes) found in the DNA of cancer cells. Knowing the TMB assists the oncologist plan the best treatment. For example, tumours that have many mutations appear to be more likely to respond to certain types of immunotherapy. The TMB is also used as a type of biomarker.

Loss-of-heterozygosity evaluation (LOH)

Loss-of-heterozygosity (LOH) is the process by which a normal cell turns into a cancerous one and begins to abnormally replicate. It is one of the types of genetic mutations that can play a role in cancer development. Some genes might be lost to LOH without causing a problem. However, LOH in specific types of genes is more of a concern. These genes, called tumour suppressor genes, are very important genes for cancer prevention and they normally work to regulate the cell cycle. They make sure that the cell doesn’t replicate and divide unnecessarily.

However, when this gene does mutate and loses or reduces its function, the cell can progress to cancer, usually in combination with other genetic changes.

Researchers have discovered LOH in the PTEN gene is commonly found in prostate cancer. PTEN is a potent tumour suppressor gene, antagonizing the PI3K–AKT signalling pathway and governing fundamental cellular processes. Cancer cells cannot afford to prematurely lose complete PTEN activity, because this would trigger cellular senescence (normal cells cease to divide).

PARP inhibitors have been found to work in a percentage of men with LOH of the PTEN gene.

Homologous recombination repair (HRR)

Homologous recombination is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. It is most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks.

Cancer cells with BRCA mutations have deficiencies in homologous recombination, and drugs to exploit those deficiencies have been developed, and are now FDA-approved for breast and ovarian cancer. Olaparib, a PARP1 inhibitor, shrunk or stopped the growth of tumours in these and prostate cancers caused by mutations in the BRCA1 or BRCA2 genes, which are necessary for HRR. Cancer cells can become resistant to a PARP1 inhibitor, if they undergo deletions of mutations in BRCA2, undermining the drug's synthetic lethality by restoring cancer cells' ability to repair DNA by HRR.

It might be interesting to look at the frequency of genetic mutations that are of consequence in prostate cancer.

Incidence of Mutated Genes

Genetic Mutation	With metastatic prostate cancer	With localized prostate cancer	With no prostate cancer
BRAC2	5.4%	0.2%	0.3%
CHEK2	1.9%	0.4%	0.6%
ATM	1.6%	1.0%	0.3%
BRAC1	0.9%	0.6%	0.2%
GEN1	0.5%	0.0%	0.1%
RAD51D	0.4%	0.2%	0.1%
PALB2	0.4%	0.4%	0.1%
NBN	0.3%	0.2%	0.1%
PMS2	0.3%	0.2%	0.1%
ATR	0.3%	0.0%	0.1%

Chart: Created using data from Pritchard, CC. et al., N Engl J Med 2016

To conclude this section on genetic and precision medicine, it is clear that genomic biomarkers have started to significantly improve the detection, prognosis and risk evaluation of prostate cancer. It is time for patients to demand genetic testing to rule out the potential death sentence that some men with DNA errors might face and it is time for clinicians to acquaint themselves with the latest science and act accordingly.

Cancer Stem Cells

The first malignant cell, that gives rise to a tumour, is called a cancer stem cell (CSC). Most tumours are heterogeneous (non-uniform) – the cells in the tumour vary by phenotype and functions. CSCs, which comprise a small proportion (about 0.2% – 1%) of total cancer cells, have special capacities for indefinite self-renewal, differentiation and tumour formation. Currently, CSCs are considered to be the major cause of the failure in anti-cancer therapy, such as chemo-resistance and/or radio-resistance, tumour recurrence and metastasis. CSCs have the ability to facilitate a variety of cells in tumour tissue and can form new tumours. The apparent inability of most cancer treatments to kill CSCs has seen much research effort into the development of specific therapies targeted at CSCs. It is theorised that the reduction in tumour size by most cancer treatments is due to the killing of differentiated or differentiating cells, which form the bulk of the tumour, but do not generate new cells. Cancer treatment drugs pose a strong selective force on all types of cells in tumours, including CSCs, which are forced to evolve resistance to the treatment. The CSCs remaining in the tumour are likely to remain untouched (by retreating into a special micro-environment) and cause cancer progression over time. The tumour micro-environment includes the surrounding blood vessels, immune cells, fibroblasts, signalling molecules and the extracellular matrix (collagen, enzymes and glycoproteins).

All is not clear over the origin of CSCs - whether they come from dis-regulation of normal stem cells or from a more specialized population that acquired the ability to self-renew. Confounding this debate is the fact that many cancer cells alter their transcriptomes (instructions) to a more stem-like state to escape destruction. This characteristic of cancer cells to ‘morph’ is the reason why many therapies only work for a period of time before they become resistant to that therapy. This is also why the present trend is to offer patients multi-therapies concurrently. This is thought to ‘confuse’ the cancer cells.

Note the comments on page 347 about the drug doxycycline in combination with intravenous Vitamin C, and their ability to kill CSCs.

Signalling Pathways

A few descriptions to put into context the critical importance of signalling pathways:

Signal transduction is the process by which a chemical or physical signal is transmitted through a cell as a series of molecular events, (mostly protein phosphorylation catalysed by protein kinases), which ultimately results in a cellular response.

Proteins responsible for detecting stimuli are generally termed receptors. The changes elicited by ligand binding (or signal sensing) in a receptor give rise to a biochemical cascade, which is a chain of biochemical events called a signalling pathway.

When signalling pathways interact with one another they form networks, which allow cellular responses to be co-ordinated, often by combinatorial signalling events.

At the molecular level, such responses include changes in the transcription or translation of genes, and post-translational and conformational changes in proteins, as well as changes in their location. These molecular events are the basic mechanisms controlling cell growth, proliferation, metabolism and many other processes. In multi-cellular organisms, signal transduction pathways have evolved to regulate cell communication in a wide variety of ways.

Signalling pathways that are upregulated in stem cells and that are specific to their functionality represent a hypothetical target for drugs addressing CSCs. The fact that many forms of cancer share the same expression pattern in certain pathways suggests that targeting of CSC signalling pathways may be an extraordinary therapeutic strategy. Currently, the pathways that demonstrate therapeutic potential in stem cells are the Hedgehog (Hh), Wnt, Notch, and NF-κB pathways. Also, ABC transporters and tumour micro-environment seem to be potential targets for CSC depletion.

The Hh pathway plays a crucial role in regulating CSCs in prostate cancer by regulating target genes involved in proliferation, survival, metastasis, and auto-regulation. Five clinical trials are currently testing Hh inhibitors in prostate cancer treatment. Vismodegib is already FDA-approved and is being tested in stages 2A and 2B trials as a complimentary treatment in conjunction with the anti-androgen leuprolide acetate. Itraconozale is being used in HSPC (NCT018787331).

The Wnt signalling pathway is involved in multiple cell biological processes including proliferation, their survival, and cell differentiation. The Wnt signalling pathway also plays a critical role in self-renewal and maintenance of stem cells. About 10-20% of advanced prostate cancers harbour Wnt-activating mutations. This factor led to a recent study to conclude that patients who have Wnt-pathway activating mutations derived less benefit from abiraterone and enzalutamide when compared to patients without these mutations.[2]

Foxy-5 is a hexapeptide that activates Wnt-5a-mediated signalling. Increased Wnt-5a signalling may inhibit endothelial tumour cell migration and invasion and may decrease metastasis. Foxy-5 has been tested in clinical trials (NCT02020291 and NCT02655952) in mCRPC men who failed SOC therapies. Results are awaited. Other compounds are not far behind.

The Notch signalling pathway regulates stem cell maintenance and differentiation. It contributes to angiogenesis, proliferation, differentiation, and apoptosis. Several agents targeting Notch signalling are being trialled including the γ-secretase inhibitor (GSI), siRNAs, and mAb against Notch receptors and Notch ligands. A study (NCT01200810) combines the anti-androgen bicalutamide with GSI in men with recurrent disease after surgery or radiation.

The NF-κB pathway is upregulated in CSCs and is important for apoptosis resistance in tumour cells. It has been shown that the activation of NF-κB signalling in prostate cancer cells correlates with cancer progression, chemoresistance, recurrence, and metastasis. Thus, inhibiting NF-κB can suppress chemo-resistance, and mediate anti-tumour responses while enhancing the sensitivity of tumour cells to other anti-cancer drugs. The clinical trial (NCT02757365) is evaluating the efficiency of aspirin in preventing the occurrence of prostate cancer. Aspirin has already been shown to prevent several inflammation-related tumours. In this study, investigators are exploring the effects of anti-inflammatory therapy on progression from inflammation to prostate cancer and from androgen-dependent prostate cancer to CRPC.

Cancer stem cells express high levels of ABC transporters that protect these cells from chemotherapeutic agents, thereby contributing to multi-drug resistance. Recent studies using chemo-therapeutic drugs in combination with modulators of ABC drug transporters have shown some benefit. To date, there are no clinical trials targeting CSCs using ABC transporter inhibitors.

CSCs reside in a specialized cellular location known as the CSC niche, which provides a micro-environment that maintains a stem-like state, which controls self-renewal and differentiation. The tumour micro-environment also protects CSCs from drug-induced apoptosis, and is responsible for drug resistance. The CSC micro-environment is responsible for abnormal signalling pathway activation, including the Wnt, Hh, NF-κB and TGF-β pathways.

The excellent pre-clinical results have led to the development of clinical trials targeting these specific pathways. These trials address all stages of prostate cancer (localized, high-risk, hormone-refractory, and metastatic) as well as disease prevention. A number of older drugs like aspirin and itraconazole are included in at least one trial.

Oligometastatic Cancer

Oligometastatic cancer is seen as an intermediate stage of cancer somewhere between localized disease and widespread metastases. Functional imaging sees oligometastatic prostate cancer being diagnosed with greater frequency than ever before. However, the process and consequences of oligometastatic prostate cancer is not fully understood. This even extends to the definition of oligometastatic disease, where a clinical diagnosis made on the basis of more than 3 (or 4) extra-pelvic lesions is considered this form of the disease.

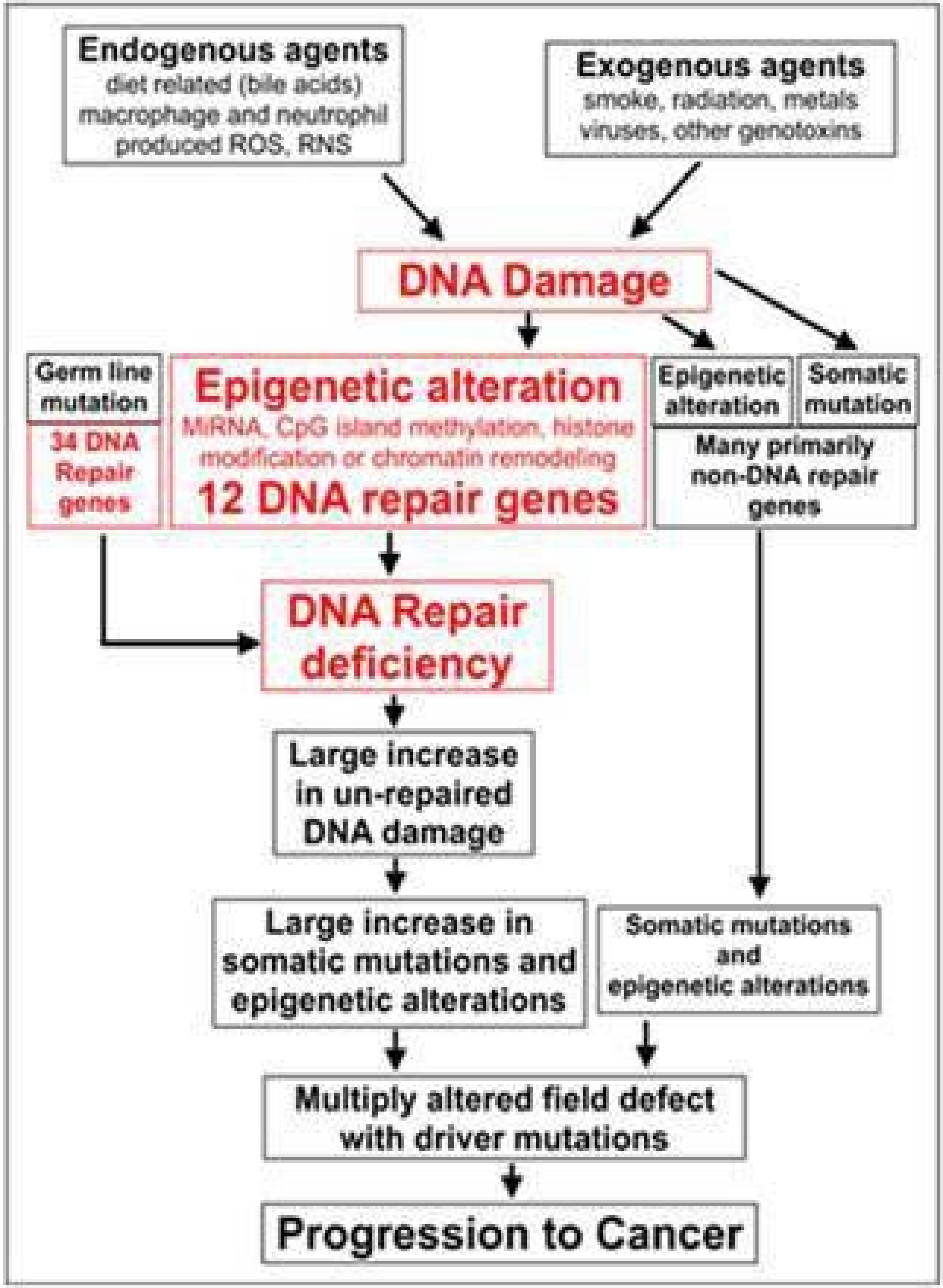
A common course of action on finding oligometastatic prostate cancer is to eliminate the individual lesions by SBRT. This reduces the cancer burden, drops the PSA and increases the patient’s confidence. Is this the best treatment protocol considering the other factors at play in this setting?

Cancer progression sees changes in the biological make up of prostate cancer. Metastatic cancer is different from high grade cancer (say Gleason 5+5) that still has to progress. At some point, the high-grade cancer undergoes a genetic transition called epithelial-to-mesenchymal transition (EMT), after which they can freely move throughout the body via the lymph and blood systems and locate themselves in distant locations where they accumulate. The microscopic metastatic cells often circulate for a long time before planting themselves in a new location. The tissue environment in the new location (especially bone tissue) often facilitates clumping and proliferation. A 1999 study found that in men who have had a radical prostatectomy, biochemical recurrence of the cancer occurred in 35% of men. The median time from PSA elevation (> 0.2 ng/ml) to detection of bone metastases was 8 years with 63% metastases-free at 5 years.

A number of randomized clinical trials are presently underway to evaluate the present standard of care for oligometastatic men (ADT). Of note, is the ongoing Phase 2 trial at the MD Anderson Cancer Centre, (NCT01751438) comparing best systemic therapy (essentially ADT) to best systemic therapy plus cyto-reductive prostatectomy (an experimental surgical approach to metastatic prostate cancer) or radiation therapy. The study will report in 2020.

To further complicate therapy choice, some oligometastatic lesions quickly progress to widespread metastases; others metastasize gradually, and others lack the capacity to progress beyond their current state. This further confirms a spectrum of biologies are at work and demands constant medical supervision.

Some men with oligometastatic cancer are inclined to take their treatment into their own hands (outside SOC guidelines), by having a cyto-RP, followed by Zytiga (or docetaxel) + ADT+ prednisone + SBRT. This all-out assault on the cancer often leads to a significant period of undetectable PSA.


Endogenous agents
diet related (bile acids)
macrophage and neutrophil
produced ROS, RNS
Exogenous agents
smoke, radiation, metals
viruses, other genotoxins
DNA Damage
Germ line mutation
34 DNA Repair genes
Epigenetic alteration
MiRNA, CpG island methylation, histone modification or chromatin remodeling
12 DNA repair genes
Epigenetic alteration
Somatic mutation
Many primarily non-DNA repair genes
DNA Repair deficiency
Large increase in un-repaired DNA damage
Large increase in somatic mutations and epigenetic alterations
Somatic mutations and epigenetic alterations
Multiply altered field defect with driver mutations
Progression to Cancer

The central role of DNA damage and epigenetic defects in DNA repair genes in carcinogenesis.

(Image courtesy of Bernstein0275 - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=25317996)

Lymph Node Involvement

What is a lymph node? A rather technical, but important description follows:

A lymph node (or lymph gland) is an organ of the lymphatic system and the adaptive immune system. Lymph nodes (LNs) are widely present throughout the body and are linked by the lymphatic vessels as a part of the circulatory system. LNs are critical to the proper functioning of the immune system, by acting as filters for foreign particles and cancer cells in the lymph fluid and to identify and fight infections. In order to do this, LNs contain lymphocytes, a type of white blood cell, which includes B cells and T cells. These circulate through the bloodstream and enter and reside in LNs. B cells produce antibodies. Each antibody has a single pre-determined target, an antigen, that it can bind to. These circulate throughout the bloodstream and if they find this target, the antibodies bind to it and stimulate an immune response. Each B cell produces different antibodies, and this process is driven in LNs. B cells enter the bloodstream as ‘naïve’ cells produced in bone marrow. After entering a lymph node, they then enter a lymphoid follicle, where they multiply and divide, each producing a different antibody. If a cell is stimulated, it will go on to produce more antibodies (a plasma cell) or act as a memory cell to help the body fight future infection. If a cell is not stimulated, it will undergo apoptosis and die.

A lymph node (LN) is enclosed in a fibrous capsule and is kidney or oval-shaped and ranges in size from a few millimetres to about 1 to 2 cm long.

Historically, men with a clinically node-positive disease at the time of radical prostatectomy (RP) often had an aborted RP and were treated with ADT alone. Men with microscopic node-positive disease at the time of final pathology, were also treated with ADT alone. ADT is not a cure and over time it fails and CRPC develops.

The management of node-positive prostate cancer is rapidly changing. Enhancements in imaging technology, particularly PSMA PET scans, are allowing clinicians to ‘see’ the LNs that are cancerous. In prior times, the identification of cancerous LNs was done mainly on size by a CT scan. A size increase was indicative of cancer being present, but not conclusively so, as infections may have caused the size increase of the LN. Some cancerous LNs don’t increase in size. Surgery improvements like a cyto-reductive prostatectomy may become mainstream over time.

An example of the advantages offered by PSMA PET scans became evident in a 31-man trial, all who had experienced biochemical recurrence after radical prostatectomy. Patients underwent ^{68}Ga PSMA PET imaging to identify potential LN metastases. ^{99}mTc-PSMA (technetium) was injected intravenously the day before surgery, and patients underwent open salvage LN dissection. After removal of all lesions visualized on ^{68}Ga PSMA PET, gamma probe measurements were used in vivo to identify additional lesions. Of 132 resected LN specimens, the gamma probe correctly classified 46 positive specimens as cancerous and 74 negative specimens as cancer-free. This method yielded a sensitivity of 84%, specificity of 100%, positive predictive value of 100%, negative predictive value of 89%, and accuracy of 93%. On follow-up, 80% of patients had ≤50% decline in PSA, and 67% of patients had complete response. The authors demonstrated the feasibility of ^{99}mTc-PSMA radio-guided salvage lymphadenectomy while cautioning the limitations of this approach for detecting low-volume microscopic disease.

This therapy is available outside a clinical trial environment in Germany. (in Hamburg by Dr. Maurer and in Munich by Prof. Gschwend who mentioned that he can remove 99% of the affected LNs detected with a PSMA PET/CT using this method).

At EAU 2019, Michael Fröhner, MD, Department of Urology, Universität Dresden, reported on their single-institution retrospective study, which provided long-term data regarding men who were node-positive at the time of RP. Of nearly 6000 men who underwent RP over a 22-year period, 527 were identified with positive LNs on final pathology. The mean number of removed LNs was 15. The mean follow-up in the surviving patients was 9.9 years.

LN density and Gleason score (8 - 10 versus < 8:) predicted prostate cancer mortality. Patients with a Gleason score < 8 and a LN density < median (11%) had a 20-year prostate cancer mortality of only 5%, whereas this rate in patients with Gleason scores 8 - 10 and a LN density greater or equal the median was 44%. The study authors concluded:

"Overall, these results confirm those of prior studies, indicating that disease biology and tumour burden are the primary drivers of progression. However, a sub-set of men with oligometastatic prostate cancer to the nodes (with low disease burden and less aggressive tumours) may be cured with surgery alone."

The STAMPEDE trial concluded in 2014. One arm of the trial looked at newly-diagnosed high-risk non-metastatic (M0) prostate cancer men receiving ADT either alone or with standard-of-care RT. Furthermore, the trial, for the first time ever, assessed the role of RT in patients with node-positive (N+) M0 disease. Results found that:

Survival for men entering the trial with high-risk M0 disease was higher than anticipated at study inception. The non-randomized data were consistent with previous trials that support routine use of RT with ADT in patients with N0M0 disease. Additionally, the data suggested that the benefits of RT extend to men with N+M0 disease.

Circulating Tumour Cells (CTCs) Re-visited

What are circulating tumour cells and what is their significance? They are cells that have shed into the vascular or lymphatic systems from a primary tumour and are carried around the body in the blood stream. Among CTCs, a sub-population constitute seeds for the subsequent growth of additional tumours (metastases) in distant organs - a mechanism that is responsible for the vast majority of cancer-related deaths. The detection and analysis of CTCs can assist early patient prognoses and determine appropriately tailored treatments.

The CTCs collected in the liquid biopsy are from the primary and distant tumour sites. The detection of CTCs is generally via CellSearch, the only FDA-approved method for counting CTCs, which is prognostic of overall survival in mCRPC. CTCs are found in the order of 1 to 10 CTC per mL of whole blood in patients with metastatic disease.

Several studies have reported that the presence of CTC clusters (two or more cells) is associated with increased metastatic risk and poor prognosis. For example, one study involving prostate cancer showed an eight-fold longer mean survival rate for patients with only single CTCs versus those with CTC clusters. If the total number of tumour cells found that meet the set size and biological criteria, is 5 or more, a blood sample is positive. In studies done on prostate, breast and colon cancer patients, median survival of metastatic patients with positive samples is about half the median survival of metastatic patients with negative samples.

A recent meta-study of scientific papers reviewing the-state-of-play of liquid biopsies concluded:

“The liquid biopsy field continues to offer tantalizing opportunities to apply new technologies towards real-time tumour profiling. These assays have great potential to transform the clinical practice of PC by providing access to real-time molecular information and by reducing the need for costly and invasive biopsies. To be sure, it is a multidisciplinary field where physicians, scientists, and engineers with different expertise work closely to develop better assays, design clinical trials, and validate the clinical utility of these liquid biopsy assays. We are hopeful that liquid biopsies will continue to advance our understanding of cancer biology and ultimately improve patient outcomes in PC.” [8]

Chapter 16.

PARP and Other Inhibitors

In this chapter, we look at various therapies that have not been discussed in detail earlier in the book as it might be easier for the reader to understand their functionality after the molecular biology and genetics explained in the previous chapter. We look at the following therapeutics:

PARP Inhibitors

Checkpoint Inhibitors

Other Inhibitors

Platinum Chemotherapies

PARP Inhibitors

In recent years, several genomic studies have identified prostate cancers with defects in DNA mismatch repair (MMR) genes. Poly (ADP-ribose) polymerases (PARPs) are nuclear enzymes playing important roles in various cellular processes including DNA repair. Tumour cells defective in either the BRCA1 or

BRCA2 genes may rely on PARP-dependent DNA repair, and therefore are sensitive to PARP inhibitors, which may also increase the sensitivity of tumour cells to DNA-damaging agents. The BRAC2 mutation is about 70% more significant in aggressive prostate cancer than BRAC1. Other genes that are sensitive to PARP inhibitors include PALB2, ATM, and CDK12.

Given the aggressive behaviour of prostate cancer in men with MMR genes, there is an urgent need to recognize this factor in patients early in their disease progression. Almost 30% of patients with CRPC carry germline or somatic alterations in their MMR genes. Thus, the treatment with PARP-inhibitor drugs are likely to deliver a real therapeutic option to a large percentage of men with CRPC with DNA repair gene mutations.

Olaparib (Brand name: Lynparza®) Manufacturer: AstraZeneca

Olaparib, a PARP inhibitor, has been approved by the FDA and European Medicines Agency registration for treatment of breast and ovarian cancer associated with BRCA 1/2 defects. Sustained responses to PARP inhibitors have also been reported in men with mCRPC with DNA-repair gene mutations. Patients with BRCA1/2 variants appear to have the greatest benefit, but men with gene mutations PALB2, ATM, and CDK12 are also responsive.

However, the science is showing us that monotherapies are generally not as effective as multiple therapies. Early studies with olaparib in combination with abiraterone are showing encouraging results regardless of mutational profile. (Side effects can be severe).

Work together with checkpoint inhibitors is also progressing with pre-clinical evidence showing that PARP inhibition may lead to adaptive upregulation of PD-L1 expression.

A considerable research effort and clinical trial activity is ongoing in the use of olaparib in certain genomic sub-sets of patients. One such example is the Phase 3 PROfound trial of Lynparza (olaparib) in men with mCRPC who have a homologous recombination repair gene mutation (HRR) and have progressed after treatment with enzalutamide or abiraterone. Results from the trial showed a statistically-significant and clinically-meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) with Lynparza vs. enzalutamide or abiraterone in men with mCRPC selected for BRCA1/2, CDK12 or ATM gene mutations, a sub-population of HRR gene mutations. At ESMO 19, a paper reported a 66% greater delay in progression than the new hormonal agents which were used for comparison in the PROfound trial. The safety and tolerability profile of Lynparza was generally consistent with previous trials.

The PROfound trial also demonstrates the potential value of genomic testing in this at-risk patient population. To this end, Myriad Genetics in August 19 filed an application with the FDA requesting the approval of its BRACAnalysis CDx diagnostic — which identifies inherited BRCA mutations — as a companion diagnostic test for mCRPC patients eligible for Lynparza treatment.

Other trials include olaparib in combination with the anti-PD-1 antibody pembrolizumab or the anti-PD-L1 antibody durvalumab. The combination of olaparib with pembrolizumab will be compared with pembrolizumab plus docetaxel/prednisone, pembrolizumab plus enzalutamide, and pembrolizumab plus abiraterone/prednisone (NCT02861573). In addition, olaparib is being evaluated in combination with radium-223 dichloride in patients with mCRPC and bone metastases (NCT03317392). Researchers are assessing which defects in homologous recombination DNA repair genes such as BRCA1/2, ATM, CHEK1, CHEK2, WES, BARD1, BRIP1, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D are suited to selecting patients with tumours sensitive to PARP inhibition.

Other PARP Inhibitors

A randomized trial Phase 3 (NCT03395197) is evaluating talazoparib in combination with enzalutamide versus placebo plus enzalutamide in men with DNA repair defects and mCRPC. At least three other trials are progressing with talazoparib in combination with other agents.

The PARP inhibitor veliparib has shown a positive response in a small study of BRAC2-mutated mCRPC patients. Other veliparib studies continue.

Niraparib (Brand Name: Zejula®) Manufacturer: Tesaro

Niraparib is being assessed as a monotherapy in a Phase 2 trial (Galahad NTC02854436) in patients with DNA repair defects and mCRPC. Four out of 10 men who had failed docetaxel and Xtandi or Zytiga, responded positively to niraparib. (Zejula reduced the tumour burden in 38% of those with BRCA1/2 mutations and gave a 62% composite response overall). This progress has lead to Zejula® being given Breakthrough Therapy status by the FDA for the treatment of mCRPC men who carry BRCA mutations and have been previously treated with taxane chemotherapy and/or androgen-receptor targeted therapy. Other trials are progressing with niraparib in combination with other agents.

Resolution Bioscience, Inc., in July 19 announced that its Resolution HRD™ liquid biopsy assay which detects homologous recombination deficiency mutations and gene deletions, is currently being used in Phase 2 and 3 clinical studies of niraparib in prostate cancer.

Rucaparib (Brand Name: Rubraca®) Manufacturer: Clovis Oncology

Rucaparib is a FDA-approved drug for BRAC2-mutated ovarian cancer, and is in a Phase 2 trial in mCRPC men with deleterious mutations in BRAC1/2, ATM and 10 other HRR genes. The FDA are fast-tracking the approval process for rucaparib, probably due to 80% of BRAC1/2 men responding to the therapy. Tumours shrank in 44% of men.

So, what’s the bottom line with PARP Inhibitors?

Get yourself a molecular profiling assay that analyses all 17 FDA guideline-recommended genes in solid tumours. Discuss any positive results with a genetic counsellor and your medical team, who might prescribe a PARP inhibitor.

It appears that it is only a matter of time before PARP inhibitors become one of the first-call biomarker-guided therapy for sub-sets of men with mCRPC. Over time their use, particularly in combinational situations, might become very significant.

Checkpoint Inhibitors

Checkpoint inhibitor therapy is a form of cancer immunotherapy currently in early-stage use and under research. The therapy targets immune checkpoints, key regulators of the immune system that stimulate or inhibit its actions, which tumours can use to protect themselves from attacks by the immune system. Checkpoint therapy can block inhibitory checkpoints, restoring immune system function.

Currently approved checkpoint inhibitors target the molecules CTLA4, PD-1, and PD-L1. PD-1 is the trans-membrane programd cell death 1 protein, which interacts with PD-L1 ligand. PD-L1 on the cell surface binds to PD1 on an immune cell surface, which inhibits immune cell activity. Among PD-L1 functions is a key regulatory role on T cell activities. It appears that (cancer-mediated) upregulation of PD-L1 on the cell surface may inhibit T cells that might otherwise attack. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction may allow the T-cells to attack the tumour.

The discovery of checkpoint inhibitor therapies led to James P. Allison and Tasuku Honjo winning the Nobel Prize in Physiology or Medicine in 2018.

Checkpoint inhibitors as a monotherapy have had very limited efficacy in mCRPC. In fact, the anti-PD-1 nivolumab failed to show responses in a Phase 1 study. Two Phase 3 ipilimumab trials in mCRPC men concluded without providing a survival benefit. However, checkpoint inhibitors have had great success with other cancers.

Researchers at the UT MD Anderson Cancer Centre found that in the tumour micro-environment of prostate cancer prior to treatment, there are very few T cells present, unlike lung cancer or melanoma. However, when they used two doses of a CTLA-4 inhibitor, the T cells were driven into the cancer. They further discovered that the tumour micro-environment adapts and upregulates other immune checkpoints, such as PD-L1, preventing those T cells that have come in, from actually killing the cancer. They then went on to combine both PD-1 and CTLA-4 inhibitors and saw pretty amazing durable responses and so was born the Checkmate 650 trial. (See below).

A Prostate Cancer Foundation-funded study published in the June 18 issue of Cell, identified a new sub-type of advanced prostate cancer that occurs in about 7% of metastatic men (versus in only 1.2% of men with primary cancer). The sub-type is characterized by the loss of the gene CDK12. Tumours in which the

CDK12 gene was inactivated, were responsive to immune checkpoint inhibitors.

“Because prostate cancer is so common, 7 per cent is a significant number. The fact that immune checkpoint inhibitors may be effective against this sub-type of prostate cancer makes it even more significant,” Dr. Arul Chinnaiyan, a senior study author and director of the Michigan Centre for Translational Pathology, said in a statement. “This is an exciting prospect for patients who have CDK12 alterations and may benefit from immunotherapy,” he added. Patients with a mutation in the CDK12 gene, and with a mutation in the second copy in the tumour, “this confers a very high probability of a complete remission with immunotherapy.” Men who had mutations in the CDK12 gene, often also had mutations in the genes CDK4 and CCND1, which are the targets of a breast cancer drug, called palbociclib. This suggests that combining immunotherapy with palbociclib could be an effective treatment for this group of men.

Pembrolizumab (Brand Name: Keytruda®) Manufacturer: Merck

Pembrolizumab was the second checkpoint inhibitor approved in the United States. In 2017 the FDA expanded its approved to include metastatic solid tumours in men with the mismatch repair deficiency or microsatellite instability genetic anomalies. So how does it work? Keytruda binds to the PD-1 receptor on immune cells and prevents the binding of the PD-L1 ligand produced by cancer cells. Cancer cells use this mechanism to evade immune surveillance, and thus, Keytruda restores a functional immune system that effectively fights cancer. Sadly, only a fraction of patients respond to checkpoint inhibitors, mainly those patients with high microsatellite instability.

Early-stage trial results of Keytruda has encouraged Merck to start a number of combinational Phase 3 trials (Keynote 365) with other cancer drugs such as olaparib, enzalutamide and docetaxel. (See below).

Nivolumab (Brand: Opdivo®) Manufacturer: Bristol-Myers Squibb)

Nivolumab is another checkpoint inhibitor, that blocks a signal that prevents activated T cells from attacking the cancer, thus allowing the immune system to clear the cancer. It is usually used in combination with the CTLA-4 inhibitor ipilimumab.

CTLA-4 Inhibitors

Ipilimumab (Brand: Yervoy®) Manufacturer: Bristol-Myers Squibb)

Ipilimumab is a monoclonal antibody that works to activate the immune system by targeting CTLA-4, a protein receptor that down-regulates the immune system. Cytotoxic T lymphocytes (CTLs) can recognize and destroy cancer cells. However, an inhibitory mechanism interrupts this destruction. Ipilimumab turns off this inhibitory mechanism and allows CTLs to function.

Enter the Checkmate 650 trial (NCT02985957) which is ongoing at five US centres. Patients in the trial receive an IV infusion of ipilimumab and nivolumab that boost the immune system. Akash Patnaik, MD, PhD, an oncologist from the University of Chicago said, “We are trying to enhance the ability of the good immune cells, the T-cells are able to enter the tumour and overcome this fortress of immune-suppression.” He went on to say that when given separately, the drugs have little effect on patients with advanced prostate cancer, but together, certain patients do very well, even dramatically responding after receiving the first cycle of treatment.

The trial had 2 cohorts of patients. Cohort 1: patients with no chemotherapy, but with at least one cycle of hormonal therapy. Cohort 2: patients with taxane-based chemotherapy, such as docetaxel. Response rate was 25% in cohort 1; 10% in cohort 2. The durability of the patient responses was a significant finding. The overall response rate (ORR) was 60% for the high TMB patients in cohort 1 and 50% for these patients in cohort 2. In cohort 1, patients with PD-L1 expression ≥1% had an ORR of 33.3% compared with 19% in cohort 2. Disappointingly, the side effects were harsh (particularly diarrhoea) and Grade 3/4 adverse events occurred in 42.2% and 53.3% of patients in cohorts 1 and 2, respectively.

Other Inhibitors

Ipatasertib (Manufacturer: Roche)

PI3K-Akt-mTOR and AR signalling are commonly negatively activated in mCRPC, with PTEN loss associated with a poor prognosis. A Phase 1b/2 study of the combination of ipatasertib, an Akt inhibitor, with the CYP17 inhibitor abiraterone in patients with mCRPC, reported superior anti-tumour activity to abiraterone alone, especially in patients with PTEN-loss tumours.

DKK Inhibitor

The DKK1 protein is often elevated in cancers, leading to more aggressive tumours, poor immune responses, and poor outcomes. The protein plays an important role in controlling the Wnt signalling pathway, a key player during embryonic development that regulates crucial aspects of cell fate and proliferation. Aberrant Wnt activity enables cancer cells to grow uncontrolled and creates an immune-suppressive environment surrounding tumours.

Thus, DKK1 inhibition might have a dual anti-cancer mechanism, causing cancer cell death directly and boosting the immune system to fight cancers. Consistently, Leap Therapeutics’s DKN-01, an anti-DKK1 antibody, has been found to have potent anti-cancer activity, working well in combination with chemotherapies and immune checkpoint inhibitors. A clinical trial started recruiting in March 19.

PLK1 Inhibitor

Trovagene’s onvansertib is a first-in-class, 3rd generation, oral and highly-selective adenosine triphosphate competitive inhibitor of the serine/threonine polo-like-kinase 1 (PLK 1) enzyme, which is over-expressed in multiple cancers, including leukemias, lymphomas and solid tumours like prostate cancer. It offers likely benefits to men who have failed abiraterone acetate/prednisone and who are also AR-V7 positive. A three-centre Phase 2 trial (NCT03414034) is still recruiting as of early September 19. Initial results received from the trial are showing great promise.

Platinum Chemotherapies

In Chapter 14, we discussed the three most common platinum chemotherapies: Carboplatin, cisplatin and oxaliplatin.

Chapter 17.

Sexual Function and Incontinence

Erectile Dysfunction

The nerves and blood vessels that control the physical aspect of an erection are incredibly delicate, and as such, erectile dysfunction (ED) often occurs even after a nerve-sparing prostatectomy or radiation therapy using even the most precise dose planning. The skill of the surgeon or radiologist can have a significant impact on obtaining a good short and long-term outcome. Men should not be shy to ascertain, as best able, the success rate and experience of the specialist/physician being considered to deliver the treatment. Perhaps surgeons with less than 250 ‘nerve-sparing’ prostatectomies under-their-belt might be considered to be too inexperienced. Men having radiation therapy should ensure that the radiation machine to be used is a recent model with software that ensures that the radiation dose is minimised to healthy tissue.

Also note your functionality after treatment can only be as good as it was before treatment. (Men with diabetes and similar illnesses won’t improve). Many men lose partial or complete ED, immediately after therapy with the majority regaining the ability to obtain an erection, hard enough for intercourse naturally or with assistance.

The Main Erectile Function Considerations

ADT, or treatments that decrease testosterone that leads to a loss of sexual drive or libido, will see their sexual drive return after therapy is stopped.

The ability to achieve a firm erection is controlled by the nerves and vessels that are intimately associated with the prostate and structures near the penis.

Orgasm/climax can be more difficult after treatment, especially if libido is low or erections are not as firm as they used to be.

Ejaculate may be minimal or non-existent after treatment, but men continue to have the pleasure sensation of orgasm without ejaculation.

Erectile Function Solutions – Chemical

Oral medications such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®), relax the muscles in the penis, allowing blood to rapidly flow in to the penis. About 75% of men who undergo nerve-sparing prostatectomy or more precise forms of radiation therapy successfully achieve an erection after using these drugs.

Another option is the placement of Alprostadil (MUSE® or CaverJect®) directly into the penis. MUSE® is a medicated pellet about half the size of a grain of rice that is inserted into the urethra through the opening at the tip of the penis. About 40% of men have successfully achieving erections after using MUSE®, but the results are often inconsistent. CaverJect® is introduced by injection and is less popular. It is important to discuss these options with your doctor.

Erectile Function Solutions – Physical

Various mechanical devices exist. A vacuum pump (sometimes called a penile pump), creates an erection mechanically, by forcing blood into the penis using a vacuum seal. Because the blood starts to flow back out once the vacuum seal is broken, a rubber ring is rolled onto the base of the penis, constricting it so that the blood does not escape. About 80% of men find this device successful, but it has a high drop-out rate. It is essential to remove the ring immediately after intercourse.

The Giddy ring has been designed by urologists to overcome many of the challenges of ED. It is an incomplete ring that is ‘tensioned’ by a rubber ring to keep the blood in the penis. It is an FDA-approved device.

A surgically-inserted penile implant can be up to 100% effective, and about 70% of men remain satisfied with their implants even after 10 years. The implant consists of a narrow, flexible plastic tube, a small balloon-like structure and a release button. The penis remains flaccid until an erection is desired, at which point the release button is pressed and fluid from the balloon fills the plastic tube, pulling the penis up and creating an erection. Note that the surgical procedure is done under general anaesthesia.

What about nerve grafts? Dr. Fausto Viterbo of the Clinic for Plastic Surgery in Sao Paulo, Brazil, pioneered the use of four nerve grafts more than five years ago. He recently said, "We put two nerve grafts in the cavernous corpus and the other two nerve grafts are connected end-to-side in the dorsalis penile nerve, improving the glans sensation, which is decreased in many ‘prostatectomized’ patients."

According to Australian researchers, micro-surgical bilateral end-to-side nerve grafts can restore erectile function and improve sexual quality of life in men who have undergone radical prostatectomy.

"End-to-side nerve grafts are based on the principle of creating new nerve pathways from a donor nerve to denervated end organs when end-to-end nerve grafting is not suitable," Dr. Christopher J. Coombs of The University of Melbourne, Australia, and colleagues explained in European Urology, (online April 19 issue).

Many urological surgeons are refining their cavernous nerve-sparing techniques during RP to improve the present ED occurrence post-surgery of about 15-40%.

For men not inflicted with prostate cancer, it's important to understand that ED is often caused by physical problems, such as poor circulation. It may also have psychological causes such as stress or anxiety which can be addressed by counselling.

I met someone at a support group meeting a year or so ago who had tried a number of ED mobile phone apps. All were considered to be rubbish, except for one called Dovetail. It walks you through a series of questions which are used to create a three-week treatment program. The relaxation and visualization exercises in Dovetail may help with psychological ED. To track your progress, the program uses the International Index of Erectile Function (IIEF-5) Questionnaire - a standard questionnaire used by doctors to categorize ED. The web site for Dovetail, also lists additional data on ED therapies that is worth reviewing. See Appendix 3 for contact details.

Incontinence

It is a fact of life that more than 25% of patients undergoing a radical prostatectomy are going to experience incontinence after their surgery. Men having other treatments for prostate cancer are not immune from incontinence. See the table of historic incontinence levels for the various treatments in Chapter 26.

In many countries the health authorities provide an incontinence nursing service which give valuable advice to patients before and after the primary treatment is provided. Their support includes the teaching of a series of pelvic floor exercises. (See previous page).

Men with regular incontinence often resort to urinary pads to absorb their uncontrollable urination. Many find the use of these pads very restrictive to their quality of life. Their sleep patterns are disturbed by having to change pads during the night. Outings from the home are often restricted by the need to change pads. The cost of pads is another consideration.

Urologists can offer incontinent men a sling procedure, which entails the surgical placement of a synthetic mesh in the groin area to compress the urethra under it. The procedure offers a fairly short recovery and requires only a small incision in the groin (between the scrotum base and the anus).

At the AUA 19 conference in Chicago, a paper reported on the 5 year follow up of the 2nd generation AdVance XP male sling system for the treatment of post-radical prostatectomy male stress urinary incontinence. The AdVance XP, has been used in Europe for several years and recently became available in the United States. The trial of 115 men, most had an open prostatectomy and had an average time between surgery and sling implantation of 29 months, and the mean urine loss at baseline was 341 g (median, 272.0 g) on the 24-hour pad test. Among the 102 patients evaluated at 24 months, 66.7% were cured, 26.5% were improved, and 6.9% failed. At 48 months, among 60 patients, the cured, improved, and failure rates were 71.7%, 15.0%, and 13.3%, respectively. At the

5-year follow-up, 61.1% were cured, 19.4% were improved, and 19.4% failed. The mean urine loss was reduced substantially, to 24.4 grams.

The study also assessed patients using the International Quality of Life Score (IQOL), the International Consultation on Incontinence Questionnaire short form (ICIQ-UI SF), the visual analogue scale (VAS) for pain, the five-item version of the International Index of Erectile Function (IIEF-5), the International Prostate Symptom Score (IPSS), and the Patient Global Impression of Improvement (PGI-I).

Some men have solved their incontinence by use of a penile clamp. It appears to me that the Pacey Cuff is an excellent urethral control device that stops urinary leakages and reduces the dependency on absorption pads by up to 100%. According to manufacturer Pacey MedTech Ltd., the cuff is more comfortable than traditional penile clamps as it maintains consistent and effective blood flow to the penis, thus eliminating possible blood supply restriction pain

Men with more severe incontinence can opt to have an artificial urology sphincter (AUS) fitted. The AMS800 (Boston Scientific, Marlborough, MA, USA) is generally regarded as the gold standard (150,000 users) and has been an excellent innovation in the field. Studies have shown that at 60 months post-surgery, 80% of patients are still dry. At five years post-surgery, complication rates remain low with infections occurring in 2%, erosion in 5%, mechanical failure in 7%, and urethral atrophy in 7%. New AUS devices under development will be adjustable, either by a urologist adding or removing fluid to the device or by an adjustable cuff that will be Bluetooth activated.

Chapter 18.

The Plan to Successfully Fight Off Cancer

A plan to successfully fight off cancer is now considered to have seven essential components. The seven components, in no particular order, are:

Alkalise the Body

Replacement of all Silver Amalgams in the Teeth

Exercise

Adequate Detoxification

Peace of Mind

Diet and Nutrition

An Appropriate Cancer Treatment Protocol

They are all very important. With one component not being adequately addressed, the whole program is likely to fail.

Alkalise the Body

The pH scale of measurement goes from zero to 14. A number 7.0 is neutral while anything below a 7 is acidic and anything above a 7 is alkaline.

It is essential for both cancer prevention and cancer eradication to maintain the body’s pH level in an alkaline state, i.e. over pH 7.0. In fact, the body pH should be maintained at between 7.3 and 7.4. Most people with poor diets see their pH below 7, which sees their bodies acidic. Cancer cells thrive in such an environment, but die in an alkaline environment. To repeat: it is essential to maintain an alkaline body state. How do we achieve this? By doing something similar to the following:

Change the diet by eliminating the ‘bad guy’ foods referred to earlier and stepping up the intake of the ‘good guy’ foods.

An early morning glass of water with sodium bicarbonate (one teaspoon) as well as taking magnesium and potassium supplements help the alkalizing process, as does a lemon a day squeezed into a glass of water.

Regular use of a body detoxifier called Colon Depur (available from Life Integrative Medicine Inc. Wilmington, DE, USA) (or similar) looks helpful in alkalising and cleansing the body. Another more unconventional method of changing your pH level is achieved by the use of bio-magnetism. More on this below.

You need to measure your pH and continue to do so on at least a weekly basis. How would you do this? You need to monitor your pH level immediately you wake up (before you eat or drink anything). This is done by inserting a short strip of pH indicator paper under your tongue for a few seconds before comparing its colour against the colour chart on the pH paper dispenser. (pH indicator papers are available from good pharmacies (drug stores) or lab supply companies. Note that they MUST cover the pH range 6 to 8 in 0.1 steps. Most litmus papers only read to the nearest 1 pH unit which is not accurate enough.

So, what is bio-magnetism all about? Biomagnetic Pair Therapy or Bio-magnetism as it is commonly known, is a therapeutic system developed by Dr Isaac Goiz Duran, MD, based on his discovery of the first bio-magnetic pair in 1988.

How is bio-magnetism therapy applied? An experienced bio-magnetic therapist places special bio-magnets in pairs strategically on the body of patients. Always one with positive polarity and the other negative polarity. This creates an ideal pH neutral field and the harmful pathogens (fungi, viruses and parasites) cannot survive in this neutral environment (they need an acid or alkaline terrain) and hence rapidly die off.

Dr Goiz found that by using specially designed magnets (of a minimum 1000 gauss strength) that he placed in pairs (a positive and a negative) on specific areas of the body, he was able to fight harmful viruses, bacteria, parasites and fungi that were found in the body. This simple technique effectively helped literally thousands of people with all types of health issues. Many patients commented that during the magnetic treatment session, they felt an energy surge as the body reacted to the eradication of the harmful pathogens.

When I first heard about this technique, my immediate thought was ‘quackery’, but closer examination suggests otherwise. Dr Goiz has very successfully treated more than 350,000 patients with biomagnetism and has trained more than 20,000 medical doctors and other health therapists from many countries, particularly in the Spanish-speaking world.

The patient lies fully clothed on the massage table. The therapist first places the magnets on areas that need treatment which correspond to the tumours and metastasis areas of the body. The therapist then scans the whole body for pH imbalances. The bio magnets restore the body’s pH to neutral.

Biomagnetism is a non-invasive, low cost, safe therapy, with no side effects. Over 50 medical conditions positively respond in one to three treatments, some may require three to five sessions whilst a few chronic or long-term conditions may require more than five treatments. For more details see Appendix 3.

Replacement of all Silver Amalgams in the Teeth

Did you know that the silver amalgam fillings in your teeth contain 50% mercury, a known neurotoxin and carcinogen? The silver content is only 25%. Perhaps you are lucky in that your fillings might be made of porcelain which is pretty well inert in the mouth.

Perhaps as many as 100 million fillings are done in North America every year. The vast majority are silver amalgams. The FDA classifies amalgam fillings as a ‘device’ rather than a substance. Apparently, this obviates the need for testing and allows them to ignore the use of mercury within the body. Over time mercury vapours leach out of the amalgams and contributes to the body’s toxin load. The mercury vapour is absorbed through the lungs into the blood and is converted into its organic form, methylmercury. Methylmercury is 100 times more toxic to the body than even elemental mercury and is associated with a number of neurological diseases, including Alzheimer's and MS.

It is interesting to note that in Denmark, Sweden, and Norway, their use is illegal due to the high mercury content. Their use in Japan is very tightly controlled. In many countries the health authorities, often supported by their national dental associations, hold the status quo by endorsing the safety of dental amalgams and in some cases act against dentists that want these amalgams replaced by safer materials.

What does the mercury vapours do to you? Firstly, they can disrupt the body's glutathione enzyme system which plays a crucial role in fighting free radicals and preventing damage to DNA and cell membranes. It has been shown to cause damage to the linings of the arteries and nerve bundles called ganglia, particularly those near the prostate gland, thereby promoting prostate cancer. Mercury exposure can cause increased production of free radicals. We know that free radical damage to the cellular DNA is a primary contributor to cancer.

If your immune system is below par due to cancer or cancer treatments (chemo or radiation), what should you do? A biological dentist should be sought out and he or she should tell you why and how your silver amalgams should be removed and replaced. Apparently, the better such practitioners use the Huggins Protocol to do this remediation.

Exercise

Exercise is a critical component in the battle against cancer. If you are fit enough and able to do so, you should exercise every day for at least 30

minutes duration. If in any doubt as to your ability to exercise to this extent, seek professional medical advice. The exercise should be robust enough to make sure that you moderately sweat.

Exercise will help you lose weight which is generally beneficial to health. Your lymph system removes dangerous toxins from the body, but it ‘goes slow’ at night and needs kick-starting each morning. Press-ups, deep breathing, yoga or swimming gets the major lymph glands in the chest working.

Many cancer sufferers have been found to have depression. Exercise is a great pick-me-up with most people feeling more confident and content after a vigorous exercise session, probably due to their cortisol (a stress hormone) levels dropping significantly.

If these exercises are too vigorous for you, why not join 60 million of Chinese who do T’ai Chi every day. Please note that too strenuous an exercise can produces more toxins in the body. More on exercise in the next chapter.

Adequate Detoxification

An absolutely essential consideration in the battle against prostate cancer is an effective regime to remove toxins, parasites, fungus, yeasts, viruses and other nasties from the body.

The first step down this path is to eliminate all the bad foods from your diet and to fully embrace the foods that are good for you and which restore the nutritional balance of the body. This is not as simple as it seems. Obviously, it is easier if you buy your own groceries and prepare your own meals. Don’t forget you have to go organic so as to limit the pesticides and herbicides that are almost always present on non-organic produce. It is best to go through the kitchen cupboards and get rid of the ‘old dietary’ items that you should not be using.

The second task is to eliminate parasites, harmful bacteria and yeast from the body. It is best achieved by diet and by taking an appropriate enzyme supplement which contains amalyse, protease and/or lysozyme. The supplement must be able to remove the biofilm that the parasites and harmful bacteria produce to protect themselves. The enzymes should be taken on an empty stomach at least an hour before meals. The taking of a quality probiotic with meals will protect ‘good bacteria’ whilst undergoing this short-term detox. Garlic, cloves, turmeric, ginger, oregano, grapefruit, thyme and cinnamon are useful in ridding the body of parasites and yeasts. The detoxifying process often causes an adverse reaction from the body with symptoms including pain, stomach cramping, and digestive upset. It’s the body’s way of removing the dead material from the body. It is important to see this process through for the duration of the detoxification period.

The third task is to get rid of the environmental household and personal products that contain unacceptable ingredients. These include cleaning products, toothpaste, body lotions, antiperspirants, plastics, etc. See Appendix 3 for a web site that identifies what you should be getting rid of.

The next task is to install an appropriate water filtering system that takes fluoride, dangerous trace metals, hydrocarbons and low-level antibiotics from your drinking and cooking water.

The liver is the detoxifying general of the body. It cleans the blood many times a minute and capture toxins and other compounds from the blood as it passes through the body’s second largest organ. All cancer sufferers have an impaired liver function due to having to neutralise the lactic acid that is produced as a fuel by cancer cells; by dead cancer cells that might be killed by anti-cancer drugs or by radiation and having to process pain killers and other toxic substances that are in the system.

The liver consists of a large number of bile ducts that process bile, toxins and waste products through to the intestines and then to the colon. As cancer cells die, they are inclined to clump together and join with cholesterol to form microscopic sized gallstones that further over-power the liver.

How do we get the liver (and for that matter, the kidneys) back into shape? There are numerous regimes available from off-the-shelf detox kits usually containing some combination of fibre (soluble and insoluble) with a chelating substance like bentonite clay, to absorb heavy metals. See the Colon-Depur Bentonite Detox (available from Life Integrative Medicine Inc. Wilmington, DE, USA). The bentonite clay seeks out the toxins with which it can bind. This includes heavy metals (mercury, cadmium, lead, etc.) and other substances with an opposite charge to the bentonite. The bound pollutant is then removed from the body by the colon or kidneys.

Chris Woollams of CANCERactive.com lists a two-day natural detox program that uses olive oil, grapefruit, Epsom salts, water and ornithine tablets. See his excellent book “Everything you need to know to help you Beat Cancer.”

It is interesting to note that almost all the alternative/integrative medicine clinics do regular coffee enemas as a routine and important detoxification treatments. Thousands more do them at home a number of times a week.

Many integrative doctors recommend daily coffee enemas to clean out the liver and gall bladder and rid the body of toxins produced during tumour breakdown during cancer treatment. Without going into the chemistry of why it works, during a coffee enema the caffeine and the palmitate salts in the coffee are rapidly absorbed in the large intestine and flows quickly into the liver. The palmitates stimulate an important liver enzyme called glutathione-S-transferase, which is capable of removing a variety of free radicals from the bloodstream.

The caffeine causes the liver and gall bladder to contract, which releasing large amounts of stored wastes into the intestinal tract and out of the body. The coffee is retained for 15 minutes which is long enough to see the blood course through the body about five times.

The literature suggests that almost all successful cancer survival cases involve a comprehensive detox regime. It is also interesting to note that the Merck Index (the medical Bible of doctors) listed coffee enemas until 1977, when it strangely disappeared. Big pharma at work again?

Peace of Mind

This subject is covered a little later in this chapter. However, what is not covered there is the question of the past underlying anger or emotional factors that probably initiated the cancer in the first instance. It is undisputed that the body contains different types of memory cells. Their short role is well documented. Whether or not they have long term past memory is unclear. A search of the alternative medicine literature sees memory cells or a similar memory mechanism feature on many occasions.

My brother is presently battling mCRPC. His mental strength has been fantastic. About four years ago, he sought out a specifically trained ‘mind’ doctor who dug into his past to identify traumatic events that remain unresolved in his sub-conscious. His ‘mind’ doctor is adamant that without this inner conflict being resolved, he will not be strong enough to restore one hundred percent of his health. Many health professionals agree with this point of view.

It is also important to establish a strong support network of family, friends and a medical team that you believe in.

Diet and Nutrition

Refer to chapter 20.

An Appropriate Cancer Treatment Protocol

Refer to the relevant treatment chapter or to the chapter on Alternative Therapies that follows later in the book.

Chapter 19.

Complementary Therapies

The terms ‘Complementary Therapies’ and ‘Alternative Therapies’ are often incorrectly used interchangeably. ‘Complementary Therapies’ refers to those treatments that are used together with mainstream medical practice. ‘Alternative Therapies’ refer to treatments that are outside the mainstream of conventional medical practice. These are reviewed in Chapter 21. Use of natural products, mainly in the form of dietary supplements including herbs or botanicals, minerals, vitamins and probiotics, maybe used as Complementary or Alternative therapies. In this book they are covered extensively in the next chapter on Diet and Nutrition. Mind and body practices, such as meditation, etc. also have a very important part to play in fighting prostate cancer.

After you have been diagnosed with prostate cancer, it is amazing how you become aware of many friends, acquaintances, work colleagues and others that have, or have had, prostate cancer. There are about 600 playing members of my golf club, and as a long-term member who plays twice a week, I know perhaps half of these. The majority are in the 55 plus age group; i.e. in the zone for prostate cancer. Many keep their prostate cancer circumstances to themselves, but a few were of help to me, after my prostate cancer ‘plight’ became known to them (I didn’t go out of my way to ‘publicise’ my affliction or seek pity). Three or four underwent radical prostatectomies, one had seed brachytherapy and two more had x-ray radiation. One of the RALP patients was a surgeon. I was a little surprised that he seemed unaware of the specifics of the various radiation treatments available to him or to have considered them in any way. Perhaps it was the ‘cancer anxiety factor’ at play again: get rid of the danger posed by removing it immediately!

In 2012, at about the time I was diagnosed with prostate cancer, I met Peter at a social function near where I live. Peter, a US resident, who was visiting relatives in Australia at the time, had an interesting story to relate. He had previously been diagnosed with incurable prostate cancer with metastases having set in. Five years ago, the medical profession had told him that he had better get his affairs in order as he would be dead in 12 to 18 months. At about 60 years of age, Peter was not of the mindset to accept this and committed himself to finding a way to rid himself of the cancer. His online research turned up a host of sites that provided ‘non-mainstream’ treatments for his cancer. Some of these involved complementary and alternative therapies. One of his challenges was to sort the wheat from the chaff or scientific fact from fiction. His search led him to the Prostatepedia (formerly the Prostate Forum) web site of Dr Charles ‘Snuffy’ Myers in the USA. Access it via Appendix 3.

Prostatepedia’s content was prepared by pioneering prostate cancer oncologist and prostate cancer survivor, Dr Myers (before his retirement in 2018). As a leading prostate cancer specialist, Snuffy Myers offered a non-biased look at all the available treatments. He made his analyses based on the available science—period. Peter made contact with Dr Myers and visited him in Charlottesville, Virginia in, I think, 2006. Peter was provided with a host of preparations that were to be taken daily. Each year Peter made an annual visit to see Dr Myers and return with adjustments to his treatment regime. As I understand it, some part of the treatment involved taking homeopathic substances. Each year, his PSA levels dropped or held previous levels with the metastatic progression of the prostate cancer regressing. The cost of the ‘pills’ was in excess of $25,000 a year. Rob, a golfing friend, also visited Snuffy Myers some twelve or thirteen years ago. More on Rob in the last chapter of the book.

My late brother had been diagnosed with prostate cancer some 21 years ago. He had had exposure to Chinese medicine prior to his cancer diagnosis and decided to undertake an ongoing course of herbal treatment prescribed by his specialist (who offered conventional treatment as well as Chinese herbal solutions). After 18 months of herbal treatment, his PSA was still elevated, but was not increasing. The 55 pills he took three times a day provided by his specialist were costing $10,000 per annum. At that time, he decided to take a more proactive approach to his prostate cancer treatment and moved to another urologist. In 2000, my brother came across a book titled “How to Fight Prostate Cancer and Win” by Ron Gellatley. This book was first published in 1998 by Cargel Press International and has since been reprinted a number of times. At the time the book was published, Ron was an accredited Naturopath, Clinical Nutritionist, Homeopath and Medical Herbalist who had been in practice for over 15 years. His PSA was 126 and sixty percent of his prostate was cancerous. The very well written book describes in great detail his plan to rid himself of prostate cancer over a six months period. His plan culminated in his PSA reducing to 0.07 at the time of his book going to press.

The starting point of Ron’s determination to rid himself of the threat to his life that was presented by his prostate cancer was his unshakable belief that he would succeed in his task based on the combination of a strong positive belief and the use of appropriate nutrients. His nutrient intake included Bovine Cartilage and Lactoferrin, which he suggests are amongst the most powerful anti-cancer nutrients available. He co-operated with a natural medicines company in Australia, to see the latter come up with a new product called ‘Promaxin Ultimate’. In the interim, this product has become unavailable. However, there is a multitude of high-strength herbal and nutritional male support supplements available that have been scientifically proven to provide relief of the symptoms associated with medically diagnosed benign prostatic hypertrophy. Most include Saw Palmetto which assists in inhibiting the conversion of testosterone to dihydrotestosterone (DHT) in the prostate. It also blocks the attachment of dihydrotestosterone to cellular binding sites, and subsequently increases the breakdown and excretion of dihydrotestosterone from the body. (Medical research suggests that DHT is involved in the progress of healthy cells to cancer cells).

Antioxidants and their Role in Fighting Prostate Cancer

As will be revealed below, antioxidants are very important in the fight against cancer. However, in the minds of most doctors they are ‘complementary’ agents to more mainstream treatments. Many practitioners in the ‘alternative’ camp, believe that they have a more substantial role in prostate cancer treatment.

What are antioxidants? They are a class of molecules that are capable of inhibiting the oxidation of other molecules. (Oxidation is a chemical reaction that can produce free radicals in the body that can lead to chain reactions that are known to damage cells). The body naturally circulates a variety of nutrients in the body with antioxidant properties. The body also manufactures needed antioxidants in the form of enzymes in order to control free radical chain reactions. Natural antioxidant production deceases with age which leads to increased free radical cell damage. The maintenance of appropriate antioxidant levels in older people requires an adequate diet and/or supplementation.

This leads to the question what are free radicals? Simply put a free radical is an atom or molecule that has a ‘free’ electron, i.e. it is unpaired. This ‘free’ electron sees them highly reactive. They aggressively attack other molecules (proteins) to ‘steal’ an electron to complete their incomplete pair. They are formed in the body as a result of normal metabolism and energy production. They are also produced by the body during exercise and when there is inflammation anywhere in the body. They are the body’s natural biological response to environmental toxins like cigarette smoke, chemicals, excessive sunlight, cosmic and man-made radiation. The result is damage to the body’s DNA and other cell structures. Free radicals generally collect in cell membranes, which makes the cell’s lipids prone to oxidative damage. When this happens, the cell membrane becomes brittle and leaky, causing the cell to eventually fall apart and die. This in turn, is disruptive to the duplication of DNA and interferes with its orderly maintenance.

Free radicals go on the rampage throughout the body, in the absence of sufficient antioxidants to ‘surrender’ an electron so as to halt the oxidative process. Unchecked free radical proliferation leads to poor cell performance followed by tissue degradation and increased risk of disease.

Antioxidants are nature's way of providing your cells with adequate defense against attack by reactive oxygen species (ROS). With the availability of appropriate micronutrients, the body is able to resist aging caused by its everyday exposure to environmental toxins and other pollutants. An inadequate supply of antioxidants puts the body at risk of oxidative stress, which leads to accelerated tissue and organ damage.

Numerous long-term studies have shown that the regular taking of antioxidants in supplement form has yielded reductions in specific cancers by up to 48%. Most studies were a random, blind test showing cancer occurrence or death reductions of 13 to 40%. Antioxidants have other properties which include:

An ability to hold onto dangerous metals such as mercury, arsenic and chromium, by what is called the chelation effect. These metals can be washed out of the body in the urine by this chelating effect before they create oxidative stress and cell damage.

Some such as flavonoids, can act as a virtual shield by attaching to DNA to protect it from free radical attack.

Yielding anti-cancer compounds that halt cancer growth and force some cancer cells to self-destruct (apoptosis).

Stimulating the body's genes and increase its natural defenses.

Types of Antioxidants

There are numerous types of antioxidants each of which has its place in the scheme of things. The first two types can be determined by their solubility. Some are water soluble whereas others are oil soluble. They are referred to as being either hydrophobic (lipid/fat soluble) or hydrophilic (water soluble). Both types are important as the membranes between cells are made of fats whereas the interior of the cells and the spaces between them are water filled. Free radicals attack both types of cell material, both watery cell content and the fatty cell membranes.

Lipid-soluble antioxidants are those that protect your cell membranes from lipid peroxidation. Some examples of lipid-soluble antioxidants are vitamins A and E, carotenoids, and lipoic acid. As expected, water-soluble antioxidants are found in aqueous fluids, like blood and the fluids within and around your cells. Some examples of water-soluble antioxidants are vitamin C, polyphenols, and glutathione.

Another important characterization of antioxidant types is whether or not they are enzymatic or non-enzymatic antioxidants. Enzymatic antioxidants are only produced by the body with their task being the capture and removal of free radicals from the system. This is achieved by converting the free radicals into hydrogen peroxide and then to water by a complex process of chelating with various metals.

Glutathione is considered to be the body’s most important enzymatic antioxidant as it optimizes the performance of all the other antioxidants, including vitamins C and E, CoQ10, alpha-lipoic acid, as well as the fresh vegetables and fruits that are eaten. It is present in the form of a peptide and is found in every cell in the human body. It oxygenates the cells and protects their mitochondria from oxidative and peroxidative stress damage by breaking down the hydrogen peroxides and other organic peroxides into alcohols. It assists in the removal of toxins from the cells of the body and gives cells protection from the damaging presence of chemicals, radiation and pollutants. It diminishes in the body with age which lessens its impact in fighting age-related diseases.

Fortunately, there are foods available that contain micronutrients that stimulate its natural production in the body. These foods include avocados, asparagus, curcumin, watermelons, strawberries, cauliflower and broccoli.

Perhaps the next most important enzymatic antioxidant is Alpha-Lipoic Acid or ALA. It is an excellent free radical scavenger and is one of the few antioxidants that cross the brain barrier. It helps in the fight against brain diseases such as Alzheimer's. It has other amazing properties such as reducing inflammation via its role in gene expression and is an excellent chelating agent. To top it all off, when glutathione and other key antioxidants levels are low, it acts to stimulate them to rapidly increase their production. It is similar to glutathione in its ability to stimulate glutathione and Vitamin C and E production in times of need. Yeast, liver, kidney, spinach, broccoli, and potatoes are good sources of ALA.

CoQ10, or coenzyme Q10, is another important antioxidant, which is converted by the body to its reduced form, called ubiquinol, to maximize its benefits. It is used by every cell in your body and has a role in producing ATP, a molecule in body cells that energise the cells.

Other important non-enzymatic antioxidants that must be provided by food, beverage or by supplements are:

Resveratrol: Besides being an excellent scavenger of free radicals, it has further properties that lowers blood pressure, improves the health of blood vessels and helps inhibit prostate cancer. It is found in the skin of red grapes, cocoa and red wine.

Carotenoids: A class of naturally-occurring compounds that have powerful

antioxidant properties. They give foods their distinctive coloring. There are two different groups of carotenoids these being Carotenes and Xanthophylls.

Carotenes include lycopene (found in red tomatoes) and beta-carotene (found in carrots), which is converted by the body into vitamin A. Xanthophylls are antioxidants that reduce the sign of ageing and improve heart health. The US National Cancer Institute has determined that xanthophylls stop cancer cell growth and contribute to cell death.

Perhaps the most important xanthophyll is astaxanthin. It is the most powerful carotenoid in terms of free radical scavenging being 65 times more powerful than vitamin C and 54 times more powerful than beta-carotene. It has wide ranging health benefits including its support of the immune system, reducing oxidative damage to DNA and reducing the risk of various cancers. It is found in micro-algae, yeast, salmon, and krill.

A final word: Don’t under-estimate the benefit that antioxidants can offer in the prevention of prostate cancer and in the fight against it.

The General Categories of Complementary Therapies

There are five general categories of complementary therapies (including diet, nutrition and herbal remedies which are considered separately in Chapter 20). These general categories and their sub-groupings are:

Mind, Body and Spirit

Meditation

Tai Chi

Aromatherapy

Manual and Physical Healing

Acupuncture

Massage

Exercise

Diet and Nutrition (See Chapter 20)

Supplements

Vitamins

Minerals

Proteolytic Enzymes

Special Diets

Fasting

Herbal Remedies (See Chapter 20)

Herbs and Spices

Pharmacological and Biological Agents

Homeopathy

Shark Cartilage, Bovine Cartilage

Lactoferrin, etc.

It is arguable that some of the above therapies perhaps fit better in the

‘Alternative Therapy’ stream rather than the ‘Complementary Therapy’ category. Let’s not get too hung up on semantics. There are dozens of books, some of which are excellent, that give in depth discussion on the use of the above agents or treatments. This book gives a broad overview of their use rather than a detailed investigation of their therapeutic value.

The term ‘holistic medicine’ is often referred to when considering a number of the broad groupings listed earlier. It’s all a question of what is meant by ‘holistic’. Some people might define it strictly as complementary and alternative medicine. Others might consider it a term that refers to treating the ‘whole person’ rather than treating a specific ailment or disease. There is not a doctor anywhere, who wouldn’t promote a healthy lifestyle which might include regular exercise, good eating habits, not smoking and the management of stress. Of course, claims made by some holistic health practitioners are exaggerated and/or are not supported by the current scientific literature. It sometimes doesn’t mean the claims are necessarily wrong, but that science has not yet caught up with holistic medicine. The origins of some holistic therapies, go back thousands of years. One thing that is practically certain is the fact that an increasing number of holistic treatments are becoming more common in mainstream healthcare, where they are used as an adjunct to standard medical treatment. Perhaps the correct term for joint holistic and conventional treatment is integrative care.

Why do some cancer sufferers turn to holistic, complementary and/or alternative treatments?

The need to do something positive themselves to improve their situation.

To alleviate or reduce the pain or side effects of conventional treatment.

A need to take an active role in improving their own health and wellness which might contribute to a cure alone or by using conventional medical treatment.

Mainstream treatment hasn’t worked or is thought by the patient, unlikely to work.

Cancer patients who choose alternative medicine instead of mainstream cancer treatments may be putting themselves at serious risk. They are ignoring or giving up the only proven methods of treating their disease. It is essential before embarking on a complementary or alternative therapy, to thoroughly discuss these intentions with your medical team, who hopefully are experienced in integrative medicine. This means them being experienced in ‘conventional’ and ‘complementary and alternative’ medical protocols.

Many, or even most, cancer sufferers take complementary remedies with or without their doctor’s knowledge or approval. Some of these can be safely used along with standard treatment to help relieve symptoms or side effects, to ease pain, and to improve quality of live. You should discuss their use with your doctors.

Mind, Body and Spirit

‘Peace of Mind’ was considered earlier in this chapter as one of the key elements of any plan to fight cancer. Peace of mind might mean different things to different people. To me peace of mind means living a well-balanced life in every way, with a minimum of stress in one’s life, being emotionally well-adjusted and surrounded by love, with a positive outlook on life and towards your cancer journey and if you are spiritually inclined, at one with your creator.

The issue of stress is a VERY IMPORTANT consideration in your journey to beat your cancer. The University of Malaysia discovered that chronic stress prevents the rapid creation of infection fighting T-cells and prevents quick immune reaction. Hundreds of studies over the past 40 years have confirmed that stress negatively impacts the immune system. Our bodies all contain the ‘fight or flight’ hormone called cortisol. This hormone is a member of the localised eicosanoids family. (In 1982, John Vane won a Nobel prize and a knighthood for discovering these localised hormones) Cortisol causes chronic inflammation throughout the body, the precursor to chronic illness and particularly cancer. This inflammation also encourages metastases, and it has been shown that once you develop cancer your cortisol and nor-epinephrine levels rise, causing even more inflammation.

The stress that most of us experience in our daily lives, sees the production of another class of hormones called catecholamines that also are not good for you. It is released by the adrenal glands when you are under physical and emotional stress. These hormones also damage the immune system.

According to an American Psychological Association study, there is a link between stress, cancerous tumour development, and a specific type of natural killer white blood cells called NK cells. These cells are important in fighting certain types of cancer (particularly liver, kidney, colorectal, and breast). They prevent metastasis and destroy small metastases. Stress suppresses NK-cell activity.

Epigenetics has shown that proteins called histones, can build up around DNA and block inter-cellular messages being produced. It is thought that these lost messages may cause, spread and worsen cancer. Epigeneticists, who work in the environmentally-induced genetics field, have shown that poor diet, stress, environmental toxins and hormones such as oestrogen can cause these blockages and bring on cancer.

Meditation

The word meditation means different things to different people. However, most consider it as a mind-body process that uses concentration or reflection to relax the body and calm the mind. There are numerous forms of meditation, each offering different outcomes to the practitioner. It can be self-directed or under the control of doctors, psychiatrists, mental health workers or yoga-masters. An independent panel convened by the US National Institutes of Health found that it might be a useful complementary therapy for treating chronic pain and sleeping problems such as insomnia. Some cancer treatment centres offer meditation or relaxation therapy with conventional medical care. However, available scientific evidence does not suggest that meditation is effective in treating cancer or any other disease, but rather, it may help to improve the quality of life for people with cancer.

Earlier in this chapter ‘Peace of Mind’ was considered as one of the key elements of any plan to fight cancer. Recently, I met an advanced prostate cancer sufferer who had a comprehensive plan to fight his disease. A positive mindset was considered an important element in his mind, body and spirit stance. He further believed that his conscious and sub-conscious minds must be in step with each other. To this end he had spent a number of two-hour sessions with a medical practitioner, who had assisted him achieve this equilibrium. This was only achieved after he faced up to and reconciled ‘troubled” matters in his past. He continues regular meditation sessions to ‘de-stress’ his system. The doctor suggested that without this equilibrium being reached, the cancer memory cells in the body would re-surface in the future. (Editor’s note: I am unaware of what ‘cancer memory’ cells are or if they even exist).

Tai Chi

T'ai chi, taiji or tai chi as it is referred to in English, is an internal Chinese martial art form practiced for both its defence training and its health benefits. It is also claimed to increase longevity in older people who regularly practice the art. Medical research has found evidence that t'ai chi is helpful for improving balance and for general psychological health, and that it is associated with general health benefits in older people. A comprehensive overview of the scientific literature concluded that up to 2011, t’ai chi offered no conclusive evidence of benefit for any of the other conditions researched which included cancer.[1] T'ai chi health training concentrates on relieving the physical effects of stress on the body and mind. The focus and calmness cultivated by the meditative aspect of t'ai chi is seen as necessary in maintaining optimum health (in the sense of relieving stress and maintaining homeostasis).

Aromotherapy

Aromotherapy is the use of fragrant substances, such as essential oils, that are inhaled or applied to the skin to create a feeling of well-being and good health Aromatherapy is seen by devotees as a natural way to help patients cope with stress, chronic pain, nausea, and depression and to produce a feeling of well-being. The essential oils usually used in aromatherapy might include the following oils that are produced from plants: lavender, rosemary, eucalyptus, chamomile, jasmine, peppermint, lemon and geranium. Scientific studies suggest that no conclusive evidence of benefit was apparent in preventing or treating cancer. On the other hand, proponents of aromatherapy suggest that it is of use in fighting bacterial infections; in strengthening the immune system and curing a host of maladies including cancer.

Frankincense, sometimes also known as olibanum, comes from the genus Boswellia trees, particularly Boswellia sacra and Boswellia carteri. The milky white sap is extracted from the tree bark, allowed to harden into a gum resin, and then scraped off in tear-shaped droplets. It is often referred to as the King of Oils and is thought to be one of the presents brought for the baby Jesus, by the three wise men from the east. (By the way, although I am not a religious person, I believe that the gift of gold to Jesus, was in fact curcumin, which is gold-coloured and a very expensive spice in biblical times).

In aromatherapy, frankincense oil is either inhaled or diffused via a vaporizer. It is considered a very effective sedative that induces a feeling of mental peace, relaxation, and helps relieve anxiety, anger, and stress.

Frankincense oil is said to promote healthy cell regeneration and assist in keeping existing cells and tissues healthy. The health benefits of frankincense oil are mostly attributed to its anti-inflammatory, antiseptic, disinfectant, digestive, and diuretic properties. Scientists have determined that there’s a component in this oil that not only stops cancer from spreading, but also induces cancerous cell death.

Manual and Physical Healing

Acupunture

Acupuncture has been a key component of traditional Chinese medicine (TCM) for thousands of years. Today TCM is regarded as largely pseudoscience, with no valid mechanism of action for the majority of its treatments. However, there are a large number of devotees to the practice, including Western-trained doctors. The apparent effectiveness of acupuncture relies on stimulating specific acupuncture points which corrects imbalances in the flow of qi or Ch’i as it is also known (life energy or energy flow) through channels known as meridians.

A number of systematic reviews of randomised clinical trials (RCT’s) using acupuncture for cancer pain, found that the number and quality of the RCT’s were too low to draw definitive conclusions or provided insufficient evidence to determine acupuncture’s effectiveness in cancer pain management.[2] The literature suggests that acupuncture has its place in management of the symptoms flowing from advanced cancer and/or its treatment rather than the cancer itself.

Massage Therapy

Massage therapy includes many different techniques in which practitioners manually manipulate the soft tissues of the body. These practices are designed to relax and de-stress the recipient.

Exercise

Physical activity is vitally important to your overall health and quality of life. Today, many medical specialists encourage their patients to be as physically active as possible during their cancer treatment. Regular exercise is likely to provide a host of benefits that might include:

Keep or improve your physical capabilities

Improve your confidence, self-esteem and emotional state

Keep muscles from wasting due to inactivity

Lower the risk of heart disease or osteoporosis

Lessen symptoms of tiredness (fatigue)

Keep your weight in check

Improve your quality of life.

Of course, some treatments, such as a radical prostatectomy, limit the patient's capability to exercise for a while. It is important to follow the medical team's directions as regards post treatment exercise.

The place of exercise in maximising the fight against cancer is now considered to be one of the seven essential pillars in successfully fighting the disease.

The literature varies as to what constitutes adequate exercise, both in duration and intensity. Our capacity to cope with intense or even moderate exercise varies from person to person. What I try to do is to have a reasonably vigorous walk for 45 minutes three or four times per week. I play golf twice a week which substitutes for two of the walks. However, bearing in mind what follows next, I might have to re-think this regime.

Recent research published in Cell Metabolism reported active mice experiencing a 50% reduction in tumour growth compared to inactive mice. (The metabolism of mice closely resembles that of humans). The researchers determined that with high intensity exercise, adrenaline is released into the blood stream together with natural killer (NK) immune cells. The NK cells attacked any tumours found.

Another research program found that the immune signalling molecule, called IL6, which is released by muscle tissue under heavy exercise loading, helped the NK cells, under the influence of adrenaline, to be guided to tumours.

Dr Daniel Galvao, Co-Director of the Edith Cowan University Health and Wellness Institute, recently suggested in an interview with Prostapedia, the importance of both aerobic and resistance exercises to prostate cancer sufferers. This again suggests that my exercise routine needs the addition of a resistance component.

A leading urologist who reviewed the draft of this book, was very vocal on the critical importance of all prostate cancer sufferers having a regular exercise program and sticking to it with a passion.

The importance of exercise extends beyond the benefits outline on the previous page. The key importance of exercise is to oxygenate the cells of the body. We have learnt in this book that oxygen is the enemy of cancer cells and the importance of maintaining an optimised aerobic (oxygen rich) environment in all body cells.

Diet, Nutrition and Herbal Remedies are covered separately in the next chapter.

Pharmacological and Biological Agents

Homeopathy

Homeopathy is a system of alternative medicine that involves treating the patient with highly diluted substances that are designed to trigger the body’s natural healing capabilities. The practice is based on the principle of treating ‘like with like’. For example, the symptoms created by a high dose of a compound, might see these symptoms counteracted by administering a much weaker or highly diluted amount of the same compound. The use of homeopathic remedies or the use of supplements is happening at unprecedented levels. A 2006 study tested 5 Indian-sourced homeopathic remedies against MAT-LyLu prostate cancer cells in rats over 5 weeks. The small study concluded that the remedies had no direct cellular anti-cancer effect, but appeared to significantly slow the progression of cancer and reduce cancer incidence and mortality in the target rats.[22]

Shark Cartilage, Bovine Tracheal Cartilage

A best-selling book published in 1992 titled “Sharks Don’t Get Cancer” convinced many people that the taking of ground shark cartilage as a food supplement might ‘protect’ them from cancer. However, it has been proven that many species of shark do get cancer and that there is no strong scientific evidence that shark cartilage is useful in treating or preventing cancer or other diseases. The proponents of the use of shark cartilage, as an anticancer agent, refer to the research that details its ability to stop or slow angiogenesis, the process of blood vessel development. Cancer cells rely on rapid blood vessel development for their survival and propagation.

Prior to the book referred to earlier being published, bovine tracheal cartilage consumption as a food supplement was higher than that of shark cartilage. Its proponents believe it to have similar angiogenesis properties to the shark cartilage. Additionally, it is thought to have immune system stimulating capabilities. Since the early 70’s, at least a dozen clinical trials of cartilage as a cancer fighting agent have been concluded (or are still ongoing). Only 7 of these trials have had their results published in peer-reviewed journals.[4] Results of these clinical trials appear to be inconclusive as to the benefits provided by both types of cartilage. Clinical trials and research are ongoing.

Lactoferrin

As babies, we were all first exposed to lactoferrin immediately after birth when we started being breast-fed by our mothers. It is an iron-binding protein found in the colostrum (new mother’s milk). There is about seven times the quantity of lactoferrin in early mother’s milk in humans (and cows) than exists later in the breast-feeding cycle. It is thought to protect the new born against bacterial infections and disease. Lactoferrin is produced in the exocrine glands of the body and is found in fluids of the eye, the nose, the intestines and elsewhere. It appears to have two immune-boosting functions. Firstly, it binds with iron in the blood to deprive any iron-hungry cancer cells of one of the substances that facilitates their growth. It also has the ability to release iron when necessary which makes it an excellent anti-oxidant. It is able to mop up free radicals that are coursing through our bodies at any one time. Free radicals are thought to be responsible for, or a catalyst in, the ageing process and diseases like arthritis and cancer.

Research has also identified lactoferrin as an anti-carcinogenic substance.[5] It has also been found in animal experiments, that 'iron-saturated' bovine lactoferrin is a potent natural adjuvant to augment cancer chemotherapy.[6] Lactoferrin is available, as a supplement, from health food outlets.

Summary - Complementary Therapies

In this chapter, many treatments, compounds, and mindsets are considered (referred to below collectively as ‘agents’). It is fair to say that many people benefit considerably from the use of one or more of these ‘agents’. Of course, some people might benefit more than others from a specific ‘agent’. It is also evident that some of these ‘agents’ also provide benefit as regards prostate cancer. They might prevent or delay its onset; they might minimise its severity and in some cases lead to the cancer going into remission.

Many good books are available that tell the story of complementary (and indeed, alternative) therapies for prostate cancer.

Chapter 20.

Diet and Nutrition

I believe that diet and nutrition is so important that it deserves its own chapter. In chapter 18, I referred to the seven key components in the plan to beat prostate cancer which to remind you are:

Alkalise the Body

Replacement of all Silver Amalgams in the Teeth

Exercise

Adequate Detoxification

Peace of Mind

An Appropriate Cancer Treatment Protocol

Diet and Nutrition

In this chapter we will review:

Food – Bad Guys and Good Guys

Herbal Remedies

Supplements

Minerals

Special Diets

Not all medical professionals think that diet and nutrition is important in the battle against cancer. In 2014, my brother saw a new specialist, a professor of oncology, to get a second opinion on his condition. My brother asked him what his view was on him drastically restricting his intake of all sugars so as to deny the cancer cells of glucose. He said: “Diet has no impact at all on your ongoing condition.” Now this might be due to his cancer having reached the metastatic castration-resistant stage. However, the literature is very clear. There are numerous studies that confirm that an appropriate diet gives men some protection from becoming victims of prostate cancer and even contributes to its regression in men with the disease.

Regrettably, most doctors in Western medicine today are legally not allowed to offer non-establishment approved treatments, or choose not to do so, for various reasons including lack of knowledge. This circumstance can have fatal consequences for many men with metastatic prostate cancer. In 2019, such sufferers just don’t have to accept this likely death sentence.

Prostate cancer is regarded as a genetically-originated cancer. It is very important to deny the cancer cells access to the ‘fuel’ that they thrive on. It is also important to provide the body with the micro-nutrients that fortify the body against free radical attack, and to prevent the resulting inflammation which might go on to form cancer.

We all know that some foods are good for you and others far less so. In fact, some foods are bad for you, particularly when taken in excessive quantity. It’s a case of the Bad Guys and the Good Guys.

Food – The Bad Guys

Some foods are bad for you whether or not you have prostate cancer. If you don’t have cancer an appropriate diet is likely to fend off any cancer that might start to develop. Remember that every one of us have cancer cells in our body every day. They are waiting for the immune system to miss them and/or a catalyst to triggering their uncontrollable growth.

Wherever possible remove non-organic foods from your diet, to limit the ingress of pesticides, herbicides and other enviro-toxins. In this book, it is sufficient to just identify the ‘bad guys’ without going into extensive details as to why they have been included.

Sugars

It is essential for all of us to limit our sugar intake in all its forms. Sugar is found in numerous formats including sucrose (common white or brown sugar usually sourced from beets or sugar cane); glucose (also called dextrose); fructose (commonly made from corn syrup); maltose (sourced from barley and other grains), and lactose (found in milk). Most of these sugars convert into glucose when absorbed by the body.

We have heard many times in this book that glucose is the food of the cancer cell. It is ESSENTIAL to deprive the cancer cell of it supply of food that it turns into energy by a process called glycolysis. This energy production process releases lactic acid, which is absorbed by the liver and converted into glucose, thus fuelling the cycle. Lowering sugar intake lowers the blood sugar levels, insulin production, oestrogen and IGF-1 levels – all of which work against cancer cell growth.

Foods with high sugar levels include sweets, confectionery; soft drinks; jams; ketchup and other sauces; breakfast cereals; breads; honey; cakes; white rice; fruit juices; sports drinks, pastas and pizzas, etc.

To repeat, it is CRITICAL that all cancer patients take urgent action to dramatically reduce their intake of all sugars and sugar-containing foods. It isn’t easy. In fact, it is VERY DIFFICULT and you need your family to assist you in this attempt to rid yourself of all sugars.

Dairy Foods

Conventional advice is that all dairy products should be avoided as they create the following negative circumstances:

The hormone Insulin Growth Factor 1 (IGF1), found in all dairy, causes cells to grow rapidly. Research has shown it contributes to uncontrolled cancer cell growth.

Unless the dairy is completely organic, it is likely to contain nasties such as hormones, antibiotics, pesticides and herbicides which are generally inflammatory within the human body.

The high levels of fat and protein in dairy reduce the absorption of zinc and other essential minerals, which are necessary to fight cancer.

The absorption of Vitamin D, potassium and magnesium is compromised by the protein and high calcium levels in cow’s milk.

If you have to have dairy products in your diet, make sure that the dairy is from organic, grass fed sources, rather than from ‘factory-style’ farms. Organic milk has much higher omega 3 fatty acid levels, more vitamin E, higher iron concentration and lower omega 6 fatty acids, as well as 40 percent more conjugated linoleic acid (CLA), which has been found to have a wide array of important health benefits, from fighting cancer to decreasing insulin resistance.

However, very recent research has suggested that dairy products have little or no part to play in the initiation or propagation of prostate cancer, in both non-metastatic or metastatic men.

Other research by Dr Sarah Lewis and colleagues of the University of Bristol, reported in 2017 on their review of 172 studies and trials that considered the possible link of milk or other dairy products to prostate cancer. Their particular focus was on identifying a potential mechanism for this link - the insulin-like growth factor (IGF) pathway. (IGF1 is a protein that interacts with cells, causing a cascade of chemical reactions in the cell that result in cell growth and multiplication). In summary, they found some evidence that parts of the IGF pathway may be stimulated by milk intake, and that IGF proteins circulating in the blood may increase prostate cancer risk.

In May 19, Vasconcelos A., et al., in a comprehensive review of the literature[1], reported that there is a direct relationship between mTORC1 activation and prostate cancer and that several components in milk/dairy products, when in high concentrations, increase signalling of the mTORC1 pathway. However, there are no studies showing an unequivocal relationship between milk products, prostate cancer initiation and/or progression. They concluded: “It is possible to establish a relationship between the consumption of milk products and the progression of prostate cancer. We also found a possible association with prostate cancer initiation; hence it is likely that the intake of dairy products should be reduced or minimized in men’s' diet.”

I think that collectively the research data suggests caution in dairy consumption, especially high fat products.

Red Meat

Some animals are reared in what might be considered a natural or organic environment. This should see the meat without contamination from pesticides, antibiotics and possible influences from the animal being feed genetically-modified feeds like corn. Red meat is also prone to increase the acidity in the body which is not desirable. Did you know that some red meats are sprayed with a colourant to make them look more appealing on the supermarket shelves? Perhaps the most important reason to limit red meat consumption is to reduce free radical activity in the body. The saturated fats in animal meat contribute to free radical activity with its attendant cellular inflammation. Bear in mind that in the Northern Hemisphere, most beef is a product of concentrated animal feeding operations (CAFOs) with pathogenic bacteria being ever present in a significant percentage of animals.

Finally, barbecuing meat is a favourite pass time in many countries. Burnt or overcooked meat sees dangerous nitrosamines being formed, which are a known carcinogenic compound.

Fats and Oils

The human race has been consuming vegetable fats and oils produced from plants for thousands of years. In the Mediterranean the olive is supreme. In the Pacific and in parts of Asia, the coconut provides its oil from the white flesh of the fruit. (Coconut oil is a great anti-dementia or anti-Alzheimer’s agent).

A more modern phenomenon is the hydrogenation of a whole host of vegetable oils such as oils from the sunflower, rapeseed/canola and corn/maize. They are heated to very high temperatures in the refining process that extends their life in pantries, supermarket shelves and in the fast food industry. Without hydrogenation these oils would quickly go rancid and would have to be thrown out. Unfortunately, a host of other substances are used in the hydrogenation process that often leave undesirable chemical traces.

Oils that go through the hydrogenation process are referred to as transfats. They are very bad for you. Research has conclusively shown that people with a high transfat intake are at higher risk of a heart attack and also memory impairment. Various research studies have shown increased consumption of transfats has led to higher level of colorectal and pancreatic cancers.

How do transfats damage the body? Simply put, transfats stimulate the production of prostaglandins in the body which in turn increase inflammation in body tissue, leading to increased risk of heart attack, cancer and other serious diseases. The molecular structure of transfats sees them scavenge molecules (oe electrons) from other substances in the body. This sees the generation of large quantities of free radicals that are looking to replace their ‘stolen’ molecules (or electrons). This can lead to genetic or DNA damage.

I had a pie at the half-way house at my golf club a few months back. I checked the food label on the wrapper after eating the delicious pie. One gram of transfats. I have eaten my last pie! It is essential to limit free radicals forming in the body and that requires the elimination of transfats from the diet.

As long as they have not been through the hydrogenation process the following oils are good for you: olive oil, flaxseed oil; coconut oil; fish oil; linseed oil, evening primrose oil and oil pressed from nuts such as almonds, cashews, brazil nuts, hazelnuts, and pumpkin seeds.

For a comprehensive coverage of oils and fats, read Chris Woollams’ book, “The Rainbow Diet.”

Processed Foods

Processed foods include the ‘sandwich’ meats (Devon, smoked ham, chicken, salami, etc.), sausages, bacon, dried meats, chicken nuggets, pizzas, packaged meals, packaged soups, white rice, biscuits, crisps, snack foods, most breakfast cereals, and many more. Don’t forget pretty well the entire fast food industry. They all suffer from one or more of the following:

Too much salt added (to enhance taste)

Too much sugar added (to enhance taste)

Too many additives and preservatives

Over refining which remove the ‘goodness’ (e.g. removal of vitamins, magnesium, iron and fibre from flour)

Some medium to high temperature baking processes see dangerous acrylamides formed.

Most salt in processed foods is in the form of sodium chloride, sodium nitrate or nitrite, or monosodium glutamate (MSG). The average New Yorker has been reported to consume about 20 grams of salt a day versus health authorities around the world suggesting a healthy limit of between 1 and 6 grams per day.

Research has proven a link between excessive salt intake and various cancers. It is known that excess sodium in the body has a detrimental impact on the membranes of all body cells. It limits the absorption of essential minerals in almost all body cells. It also limits the availability of the preferred potassium to the mitochondria who use it in their energy production process. Sodium works far less efficiently in this process. Excess use of sodium creates an acidic environment in the cell versus an alkaline environment in cells with adequate potassium levels.

Your diet should limit the intake of sodium and increase the potassium levels in the body. This is achieved by replacing processed foods with fresh, organic foods that are high in potassium. Some foods that match this requirement are: potatoes, lentils, broad beans, bananas, fresh fish, various nuts, green leaf veggies, brown rice and lean organic meat.

Breads

All breads are not created equally. Some are good for you with the rest of questionable value. However, all breads have a high glycaemic index (GI). On digestion, bread sparks a quick and substantial spike in blood sugar and insulin production. Research published in the “American Journal of Clinical Nutrition” reported that eating two slices of white whole wheat bread spiked the blood sugar level by more than consuming 6 teaspoons of white sugar!

Why is this so? Almost all the carbohydrates in wheat contain a compound called amylopectin A – it is unique in just how rapidly it transforms into glucose. Glucose is the food of kings for cancer cells. Amylopectin A has another nasty surprise for us. It triggers the production of small dense LDL cholesterol particles. People with high levels of these particles in their blood are considered to have a 300% greater chance of experiencing a heart attack according to a study published in the “Journal of the American Medical Association.”

Wheat-based breads contain another compound called wheat germ agglutinin (WGA) which can have direct toxic effects on most tissues in your body, including the heart and brain. WGA also disturbs the immune system and causes inflammation in body tissue. WGA is present in whole grain and even ‘sprouted’ grains.

Perhaps the answer is to eat gluten-free bread. I'm afraid not. Gluten-free breads contain a lot of nasties including chemical preservatives, soy protein, dough conditioners, industrial seed oils, corn and rice syrup and often, GMOs. The GI of various gluten-free breads is even higher than in whole wheat breads.

I came across a company in the USA called BetterBreads™ who have produced a recipe book for breads that do not contain all the nasties referred to above. It's available online for US$14. Access details of it via Appendix 3.

Artificial Sweeteners

Many readers might reduce their sugar and fructose intakes by using artificial sweeteners to starve their cancer cells of their preferred food: glucose.

Initially, I thought I would not include artificial sweeteners in the book as I didn't think these products were a factor in cancer. Further reading and research has now suggested otherwise. It is clear that at least one artificial sweetener called sucralose (Brand Name: Splenda), has been found by researchers at the Ramazzini Institute to be a factor in leukaemia. The findings prompted The Centre for Science in the Public Interest to downgrade Splenda from its 'safe' category to one of 'caution'. This has now been upgraded to the 'avoid' category.

Most of the artificial sweeteners on the market, do not lead to weight loss, but in fact the contrary. One exception appears to be Stevia, a natural sweetener derived from the South American stevia plant. It is available in tablet or powder form and is sometimes mixed with xylitol, a reasonably safe, mildly beneficial sugar alcohol.

Alcohol

A study published in the July 2009 issue of Cancer, which included more than 10,000 men, found that those who drank heavily were more than twice as likely, compared to less heavy drinkers, to develop high-grade prostate cancer. There was no difference in prostate cancer risk between non-drinkers and those who drank moderately. Heavy drinkers were defined as those who drank 50 grams (1.7 ounces or four tots) of pure alcohol a day five or more days a week.

Conversely, it is considered that the resveratrol in red wine, being an excellent antioxidant, is beneficial to the prevention of cancer cause. Patients with prostate cancer are generally advised to limit alcohol to only one or two drinks a week, probably because alcohol converts in the body to acetaldehyde, which is a known carcinogen.

Eating Out

Almost all restaurants use ingredients that the cancer sufferer should not have in their diet. Obviously, some ingredients and foods are more concerning than others, with Chinese and Asian restaurants including MSG (monosodium glutamate) in most dishes. Pretty well all eating out on a regular basis should be off the agenda, with fast foods completely forbidden.

Foods – The Good Guys

Fruits

There is a huge variety of fruits available that are very beneficial to us all. However, many of these fruits are grown on the other side of the world, picked unripened and stored in nitrogen or other gases, before they arrive in your supermarket sometimes weeks later. Of course, they were almost certainly grown under pesticide or herbicide control. Thus, it is important to choose local fruits that are grown in organic conditions.

Then we have the sugar content to consider. The sugar contents, in grams per 25 gram serving, are listed below for 22 common fruits:

Avocados	0.1		Pineapples	2.4
Tomatoes	0.7		Plums	2.4
Raspberries	1.0		Blueberries	2.5
Strawberries	1.2		Apples	2.6
Papayas	1.4		Apricots	2.7
Lemons	1.4		Bananas	3.0
Rockmelons	2.0		Cherries	3.1
Pears	2.1		Mangoes	3.3
Oranges	2.1		Lychees	3.8
Peaches	2.2		Grapes	4.1
Kiwis	2.3		Dates	17.0

One benefit of fruits is that they contain fructose, a natural sweetener that has a slower rate of digestion than most other sugars. They generally do not cause the wild blood sugar spikes that sucrose can cause. However, they do add to the daily sugar intake and their addition is a trade off against their nutritional benefits.

Brief comments follow on some of the fruits included above:

Blueberries

They are often regarded as a ‘superfood’. They are loaded with vitamins, minerals and fibre. They contain numerous flavonoids and anthocyanins (both considered good for you) and they have strong antioxidant properties.

Strawberries

They are an excellent source of vitamin C which makes them an excellent antioxidant and immunity booster. A phytochemical called ellagic acid - also found in strawberries - is another immunity booster.

Lemons

Lemons contain riboflavin, thiamine, copper, potassium, calcium, folate, vitamin B6, fibre, pantothenic acid and iron. All good nutrients for human health. A lemon a day assists in keeping the body in an alkali state.

Papaya

Papayas are high in vitamin C and rich in antioxidants. Their high fibre content helps slow the release of the sugar into the blood stream and assists with digestion.

Avocados

Another ‘superfood’. They contain oleic acid which is a known anti-inflammatory. It also has beneficial effects on genes linked to cancer. Holds huge store of vitamins C, B5, B6, E and K as well as folate and potassium. Also, they contain small amounts of magnesium, manganese, copper, iron, zinc, phosphorous, vitamins A, B1 (thiamine), B2 (riboflavin) and B3 (niacin).

Green Vegetables

Green veggies contain many nutrients that are known cancer fighters. The most well understood compounds are probably the isothiocyanates found mainly in the cruciferous vegetables such as cabbages, cauliflowers, kale, bok choy and broccoli including their spout variants. The most active isothiocyanate group are the sulphoraphanes. (The sulphoraphanes stimulate enzymes in the body that detoxify carcinogens before they damage cells). Two other compounds found in cruciferous vegetables called indole 3-carbinol and crambene are also suspected of activating detoxification enzymes.

A recent research study revealed that daily consumption of cruciferous vegetables reduced oxidative stress in participants by 22% over three weeks versus only 2% in a group that had no such vegetables, but a daily multi-vitamin dosage.

So, which one should you take? Brussel sprouts topped the Vitamin E, B1 and plant omega 3’s and were joint top in folate with broccoli. Kale had more than 100% of the recommended daily allowance of vitamin A. It is clear that broccoli and Brussel sprouts come out tops with kale and bok choy a close third and fourth. Cauliflower and cabbage were a distant fifth and sixth. About half of the fibre in cruciferous vegetables is super-healthy soluble fibre. It is best to lightly steam these vegetables or even nibble on them raw so as to retain their goodness. A 24-year-old published paper found that 70% or more of the studies found a link between cruciferous vegetables and protection against cancer. Today, the figure would be much higher.

A special note should be made about broccoli sprouts. They have been found to contain as much as 50 times the ‘cancer fighting power’ of fully-grown cruciferous vegetables and are packed with enzymes that assist the body’s digestion, and its metabolic, and detoxification systems.

Other Vegetables

Some doctors claim ‘an onion a day keeps the doctor away’. Rich in vitamin C, sulphur compounds, flavonoids, and other phytochemicals (also called polyphenols), onions play an important role as a prebiotic, increasing the ratio of beneficial bacteria in the gut, which is important for general health and disease prevention. Onions contain more polyphenols than leeks or garlic and are an excellent source of an important flavonoid, called quercetin. This flavonoid is a powerful antioxidant with anti-inflammatory properties that helps in regulating the immune system’s response to outside stressors.

Space doesn’t permit a detailed description of the benefits provided by the following vegetables: carrots, red, green and yellow peppers, radish, green beans, celery, beetroot, brown rice, mushrooms, squash, turnips and parsnips, etc. Tomatoes have been covered under ‘lycopene’.

Salvestrols

Salvestrols are natural fungicides (phytonutrients) found in fruits, vegetables and herbs, that have been metabolized by the CYP1B1 enzyme in cancer cells, to produce a toxin that kills cancer cells. The most well-known salvestrol is resveratrol, found in the skins of red grapes. In the book “Salvestrols: Nature’s Defence against Cancer” the author, Brian A. Schaefer, D.Phil., asked the question why is cancer so prevalent and why is the prognosis so poor, considering the salvestrol mechanism (Salvestrol + CYP1B1 + anti-cancer metabolite)? He offers four reasons: Firstly, and most importantly, a serious depletion in salvestrols in the Western diet with almost no organic fruit and vegetable consumption. Secondly, exposure to inhibitors of the CYP1B1 enzyme, thus inhibiting its performance in metabolizing salvestrols. Thirdly and to a much lesser influence, polymorphism of the CYP1B1 enzyme. Finally, the levels of CYP1B1 expression in the cancer cells.

The early picking/harvesting of the crop often occurs prior to the salvestrols being produced in quantity as natural protection against plant invaders. Research has confirmed salvestrol levels 30x greater in organically-grown produce versus those produced by modern farming practices.

It is interesting to note that the key researcher in this field is Professor Gerard A. Potter, Ph.D., who some years ago discovered abiraterone acetate, which is better known as Zytiga. The above two men have developed commercial interests that market various salvatrol tratments.

The list of salvestrol-containing foods includes: Broccoli, cabbages, kale, savoy, Brussels sprouts, cauliflower, kohlrabi, spinach, chard, lettuces, watercress, green beans, broad beans, garden peas, artichokes, red & yellow peppers, beansprouts, celery, salad rocket, avocado, pumpkins, squashes, marrows, zucchini, cucumbers, melons and gherkins. Also, all red fruits such as strawberries, raspberries, grapes:and plums plus blackcurrants, redcurrants, blackberries, blueberries, mulberries, cranberries. Also, apples, pears, pineapples and herbs such as parsley, sage, rosemary, thyme, basil and mint.

Herbal Remedies

In this section, we look at a selection of herbal remedies that are considered to have some efficacy as regards prostate cancer. The list is not a comprehensive listing, but it does contain the most popular herbs and spices such as saw palmetto, green tea, ginseng, and cinnamon, curcumin from turmeric, oregano, grape seed extract, and herbs like astragalus, essiac, echinacea, cat’s claw and flaxseed oil. They are presented in no particular order.

It is something of a paradox that both radiation and chemotherapy treatments significantly weaken the body’s immune system, when it is already under severe stress due to the progress of the cancer. Some specialists do something about this, by prescribing interleukin and/or interferon, which are called cytokines. These hormone-like products stimulate the immune system by increasing the production of white blood cells and macrophage cells which destroy foreign bodies. These cytokines are often termed biological response modifiers.

You will note regular references to immune system support mechanisms by the natural herbal cytokines that are listed below. Some of these natural products also assist the body in identifying hard-to-detect cancer cells and to remove dead cells and toxins from the body.

Most of the herbal remedies listed over the next few pages have strong antioxidant properties. The term antioxidant is a misnomer. It does not mean anti oxygen. These substances do not ‘stop’ oxygen, but are rather important regulators of the oxidation processes in the body.

Saw Palmetto

Saw palmetto extract is obtained from the fruits of the saw palmetto plant (Serenoa Repens). It is said to be used by more than two million men in the USA, as a treatment to reduce the symptoms and effects of benign prostatic hyperplasia (BPH).

The berries of the saw palmetto contain chemicals, called sterols, which are thought to interfere with the ability of testosterone to cause prostate cell growth. Early studies on saw palmetto concluded that the plant extract could ease the symptoms of benign prostatic hyperplasia (BPH), or enlarged prostate, which include difficulty urinating, urine leakage and sleep deprivation due to the need to go to the bathroom several times each night. Few of these studies included a placebo control group. A number of recent clinical trials have examined the efficacy of saw palmetto versus a placebo and/or one of the two most popular drugs (finasteride - Proscar®), and (tamsulosin - Flomax®) which are prescribed for diminished urinary flow due to the narrowing of the bladder neck caused by BPH. These recent trials/studies have used more reliable methodologies, which have found that the plant extract was no better at alleviating symptoms than taking a placebo pill.[2] Men taking finasteride or another 5α-reductase inhibitor (5-ARI), also known as a dihydrotestosterone (DHT) blocker, should be aware that their PSA values are significantly under-reported. Many doctors are unaware of the fact that the PSA should be adjusted 50% higher, when a 5-ARI is being used.

The American Cancer Society is quite unequivocal about saw palmetto: “Available scientific studies do not support claims that saw palmetto can prevent or treat prostate cancer in humans.” Some doctors ask men having their first PSA test to go off saw palmetto prior to having the PSA test so as to establish a true baseline result. This recommendation is made as saw palmetto affects testosterone metabolism, as do finasteride. This drug does affect PSA results, but saw palmetto does not appear to do so.

Green Tea

The Chinese have been drinking green tea for 3000 years and it also has been used in other Asian countries for nearly 1000 years. In recent years, there have been a number of significant studies into green tea and its therapeutic values. Some of these studies have shown the polyphenols in green tea to act against cancer cells in cell cultures.[3] It has been postulated that epigallocatechin (EGEC) compounds in the tea may inhibit new blood vessels from forming, thus restricting cancer cell growth. The initial studies have yielded mixed results. This has prompted the FDA to review all published studies. For a number of years, the FDA has been involved in a dispute with a green tea supplier. In 2011 it announced its conclusion in this matter which stated:

“Green tea may reduce the risk of breast and prostate cancer. (The) FDA does not agree that green tea may reduce the risk because there is very little scientific evidence for the claim.”

There are many thousands of cancer sufferers who would not agree with this statement, based on their own positive and practical experiences.

Cinnamon

Produced from the bark of the evergreen cassia cinnamon tree grown in SE Asia, it has a positive impact on diabetes sufferers. It has strong anti-inflammatory capabilities as well as it is likely to assist in erectile dysfunction. It helps regulates insulin sensitivity that yields an indirect benefit by providing less glucose to voracious cancel cells.

Turmeric and Curcumin

Turmeric is a plant that is grown in the tropical parts of India and Asia. The active constituent of the turmeric root is the bright yellow curcumin and is the main spice in curry foods. It has powerful anti-inflammatory and antioxidative properties. In addition to these beneficial properties, it is a powerful weapon against cancer. Research studies have shown that this super spice can actually prevent cancer tumours from developing. One of many mechanisms as to how curcumin works, is by reducing pro-inflammatory immune-modulators including Nfkb and the cytokines CXCL1 and CXCL2 that all can contribute to cancer formation. Lower pro-inflammatory markers lower PSA values. In those who already have cancer, turmeric slows the growth and spread of cancer. In a research study done with mice injected with cancer cells, the curcumin in turmeric was proven to be more than twice as effective as the cancer drug paclitaxel (Taxol®). Numerous other research studies have sited the benefits of curcumin, but many of these studies has seen the curcumin taken by intravenous injection. Most curcumin supplements offer less than 10% bioavailability of the curcumin to the body as they are not water soluble, thus limiting its absorption into the bloodstream. Dr Geo Spinosa, author of the quality book “Thrive Don't Only Survive: Dr.Geo's Guide to Living Your Best Life Before & After Prostate Cancer” recommends 1000 – 2000mg per day, but notes that up to 8000mg per day have been considered as being safe. (Discuss dosages with your medical professional). Recently, a reformulated version has become available that offers 100% bioavailability of its active agent to the body. Also make sure that it does not contain piperine, or even worse a Class-1 residual solvent known as EDC (1,2-dichloroethane and a probable carcinogen). See Appendix 3 for more details.

Oregano

Oregano is a medicinal and culinary herb that has been providing health benefits for thousands of years. It contains vitamins A, C, E, and K, as well as fibre, folate, iron, magnesium, vitamin B6, calcium, and potassium. It also contains antioxidative, anti-inflammatory, anti-bacterial phytochemicals. Research into the phytochemical, carnosol, found in oregano, has shown it to have anti-cancer property in prostate and other cancers. It is available as a herb, in a spice blend or as oregano oil. There are two different oregano plants. The Mexican variant and the European variety. Both have similar properties, but have distinctly different tastes.

Grape Seed Extract

Research in the USA reported in 2011, that grape seed extract was considerably more effective as an immune booster than a host of other plants and herbal extracts.

Astragalus

Astragalus is made from the roots of the herb. It has been in widespread use in China for thousands of years, to treat a wide range of maladies. The herb has been the subject of significant international research as an anti-cancer agent. Japanese research has shown it to boost interferon production and B-lymphocyte growth and T-cell, interleukin and antibody production. In a clinical trial conducted by the MD Anderson Hospital in the USA, researchers found that patients undergoing radiation therapy, who had been taking astragalus, had twice the survival rate when compared to those not taking it. Other studies have yielded similar glowing reports. Its efficacy seems to centre round its apparent ability to stimulate the immune system to see rogue cells.

Essiac Tea Mixture

This mixture of originally four root extracts originated in the North American Indian tribes in the distant past. A Canadian nurse started using it as a tea about 100 years ago. It had very beneficial impact on patients attending her free cancer clinic. The tea was generally administered 12 times a day for 10 days. Four additional herbs were added to the mixture that originally had four active ingredients being burdock root (said to decrease cell mutations and inhibit tumours. High in selenium); sheep sorrel (stimulates the endocrine system); slippery elm (rich in vitamins, calcium and magnesium); Indian or Chinese rhubarb (a known anti-inflammatory, antibiotic and anti-yeast agent that also helps oxygenate the body). The four additions to the tea were: watercress (a good blood purifier and strong antioxidant); blessed thistle (again a blood purifier and with immune boosting properties); red clover (it contains coumestrol, a phytoestrogen, which may interfere with estrogen-based cancer treatments); kelp (reduces acidity in the body). More on Essiac is available in Appendix 3.

Echinacea

A number of scientific studies have indicated that echinacea (also called purple coneflower) does provide several anti-cancer benefits. These include the increase in the production of white blood cells as well as interleukin and interferon in the body. It also has good anti-viral properties. It should only be taken for a month or so and then only under medical supervision as it has blood-thinning tendencies.

Cat’s Claw (Uno de Gato)

This herb comes from the bark of the Uno de Gato plant. It is beneficial in reducing the side effects of both radiation and chemotherapy by boosting white blood cell production. It also contains a number of different types of alkaloids, some of which help in the ‘capture and removal’ of viruses, antigens and rogue cells from the body.

Flaxseed Oil

Flaxseed oil is a source of plant omega-3 fatty acids such as alpha-linolenic acid (ALA). In animal studies, ALA has been found to inhibited tumour incidence and growth in breast and prostate cancers. They also seem to decrease inflammation. It is considered by many to be one of the world’s first superfoods. (See next chapter for Flaxseed Oil and Cottage Cheese).

Supplements

Whilst channel-surfing on TV, I came across a 60 Minutes Australia program on supplements and vitamins. The program was based on a joint investigation by The New York Times and PBS Frontline. What was most alarming was the largely unregulated state of the supplements market in the USA and the fraud being perpetrated on consumers by them very frequently not getting what they paid for in the pill or tablet. Several well-known brands were under investigation for ‘under-providing’ the active ingredients whilst others were being investigated for poor quality control. For example, one bottle of flaxseed oil capsules saw all the flaxseed oil rancid.

Another consideration aired in the program was the danger in taking more than the recommended daily allowance (RDA). In the pages that follow, I have listed RDA’s for some vitamins and other supplements. These have been sourced from the scientific literature, but it is essential that you verify appropriate RDA’s for yourself from the packaging or better still after consultation with your medical advisor.

Beta-sitosterol

Beta-sitosterol is a chemical compound found in plants such as P. africanum, saw palmetto, and some legumes. It is plant sterol and has a similar structure to cholesterol. Sitosterols are white, waxy powders with a characteristic odour. Plant sterols including beta-sitosterol, reduce absorption of dietary cholesterol and may provide anti-tumour effects by acting on the immune and hormonal systems of the body or by directly inducing apoptosis (cell death) in tumour cells.[4] Beta-sitosterol, at appropriate concentrations (16mM), has been shown to significantly inhibit the growth of PC-3 prostate cancer cells and to induce apoptosis.[5] Beta-sitosterol ingestion decreases the levels of cell cycle regulator proteins p21 and p27 in the cancer cells and an increased production of reactive oxygen species which also assists apoptosis.

Any potential user of beta-sitosterol should discuss its use with their doctor as it can lead to:

Increased risk of the severity of coronary artery disease in men with a history of heart attack

It is not recommended for individuals with sitosterolemia, a rare inherited fat storage disease. (Also, It should not be taken by women whilst pregnant or breast feeding).

This compound is listed only to show that there are pluses and minuses for many supplements. There is often considerable marketing hype behind many such materials. Many supplements claim to assist in the fight against cancer, but few actually help in fighting prostate cancer. The American Cancer Society makes the following generic comment for many of these compounds:

“Available scientific evidence also does not support (name of compound) effectiveness in preventing or treating cancer or any other disease.”

It lists a host of Herbs, Vitamins and Minerals under the Complementary and Alternative Medicine section of its web site accessible via Appendix 3. Remember that supplements are supplements and they are no substitute for having a healthy and nutritious diet.

It is important to realise that natural supplements might interact with each other or with drugs that you might be taking. Also note that the natural supplement industry is far less regulated by health authorities than the drug industry and many supplements might contain dangerous impurities or less of the active agent than indicated. It is essential to discuss natural supplementation with your medical team and to find a highly reputable and reliable supplier of your supplements.

Lycopene

Lycopene is found in tomatoes and in lesser concentrations in other fruits like pink grapefruit, guavas, papaya and apricots. Tomatoes should be cooked to see the lycopene converted to its most beneficial form as a carotenoid. It is a strong antioxidant and several scientific studies have shown a lower risk of cancer amongst high consumers of lycopene.[6]

Dr William Li in 2010 in his very significant presentation “Eat to Starve Cancer” cited a study lead by Dr Lorelei Mucci (Harvard School of Public Health) into 79,000 men followed for 10 years, which found:

“Men who consume 2-3 servings of cooked tomatoes per week have a reduced risk of developing prostate cancer by 40-50%.” I recommend you go to You Tube to view Dr Li’s presentation.

Lysine

Lysine is one of nine essential amino acids that are very important to the body’s metabolic function and are not produced by the body. The lysine that the body requires comes exclusively from the foods we eat or from supplements. It is an important building block of the amino acids that together unite to form collagen, the connective tissue between all body cells. It has an even more important function that is not always recognised: it inhibits the growth of the collagen digesting enzymes that are produced and secreted by all cancer cells. According to Dr Matthias Rath, a former colleague of Professor Linus Pauling – Nobel Laureate – and head of the Dr Rath Research Institute, lysine and vitamin C both contribute to the stability of the connective tissue (collagen) and the prevention of the uncontrolled tissue degradation. It’s a critical component in the war against all types of cancer.

Proline

Proline is another important amino acid that is a building block in collagen production. The body produces some proline, but most people are deficient in this amino acid which contributes to tissue weakness and possible disease progression. It is considered by Dr Rath as an important component in the anti-cancer battle. Source proline from meat, dairy or eggs or by supplementation.

People with liver or kidney disease should be careful not to take too much proline or for that matter any amino acid supplement, without first consulting their doctors.

Berberine

Berberine is usually found in the roots, rhizomes, stems, and bark of a variety of plants in the berberis family. Berberine has been shown to inhibit metastatic activity in prostate cancer cells. In particular, berberine is one of the few compounds that inhibits the EMT (Epithelial to Mesenchymal Transition) program which causes metastases in the bones. It has multiple actions, including reducing liver glucose production and performs at least as well as metformin; it preserves the energy production system (the AMPK pathway) and even turns it back on, thus encouraging the re-start of normal aerobic mitochondrial activity. Berberine on its own attacks and weakens cancer cells, but it also improves the effectiveness of chemotherapy by enhancing chemo-sensitivity as well as improving radiotherapy by enhancing radio sensitization of cancer cells.

Proteolytic Enzymes

We have all heard of enzymes. We even find them in laundry detergent powder. But what are they? Simply put, they are protein structures of different shapes and sizes each of which has a specific function in the body. There are more than 3000 enzymes in the body that control or speeds up more than double this number of chemical reactions within the body. They are vital to our immune system and in its fight against cancer and disease. They are essential for the following body processes among many more: digestion and nutrient uptake, immune response, cognitive thinking, and systemic cellular detoxification. Also called proteases, they are the subject of massive research activity designed to better understand disease pathways, etc.

Every day, we absorb thousands of different enzymes in the food we eat. Proteolytic enzymes are a class of digestive enzyme that break down protein into amino acids for use by the body. When taken on an empty stomach, proteolytic enzymes pass into the bloodstream and become what are called systemic enzymes. These enzymes participate in the reactions within the body's cells.

It is well known that cancer cells are hard for the immune system to detect and destroy. One of the defence mechanisms of these rogue cells is found in their hard outer shell. This thick shell, called fibrin, also makes it necessary for the high doses that are needed to penetrate in chemotherapy.

Systemic proteolytic enzymes therapy enables chemotherapy dosages to be lowered with a significant reduction in chemo side effects being experienced. It also reduces scarring of organ tissue in radiation and helps tissue recover after surgery.

Enzyme therapy also stimulates cytokine production which increased activity of NK cells and macrophages. Proteins called anti-proteinases bind irreversibly to systemic enzymes. When this happens, other anti-proteinases are stimulated and stop the function of tumour regulating proteinases, which inhibits cancer metastasis.

Three of the best plant-based proteolytic enzyme supplements include papain, bromelain and rutin. Chymotrypsin, pancreatin, and trypsin are the best animal-sourced supplements. Both forms of systemic enzymes are formulated to reach the bloodstream intact and not become dissolved in stomach acid. It is important that they be consumed on an empty stomach.

Some people adopt a high dose Enzyme Therapy in conjunction with a 16 to 18 hour fast. This approach is very beneficial to the immune system, by starving the cancer cells of all sugars and improving ketone production from body fats.

Appropriate dosages might be: For prevention: 5 to 20 g/day; cancer treatment: 20 to 80 g/day; metastatic treatment: 45 to 160 g/day. All taken in capsule form spread throughout the day.

Vitamins

A well-balanced diet with plenty of vegetables and fresh fruits provides people with the majority of their vitamin needs. The results of a USA randomized controlled trial published in 2012 of male physicians taking a daily 30 nutrient multivitamin, showed a small, but statistically significant, lower risk of all cancers combined followed over a 11 year period.[8]

Vitamin A is a very important nutrient that assists in general cell growth and bone development in the body. It is obtained from either animal sources such as egg yolk, dairy products or fish or from compounds like beta-carotene or alpha carotene which are found in colourful vegetables and fruit including broccoli, carrots, squash, apricots and leafy greens. The carotenes, from this source, are collectively referred to as pro-vitamin A carotenoids and are converted in the body to retinol, which is a form of Vitamin A. The Vitamin A is stored in the liver for subsequent use.

The published literature suggested that vitamin A (and other retinoids) may enhance the immune system, slow tumour growth, shrink tumours, and make some cancer treatments work better.[7]

Vitamin B3 is a water-soluble vitamin also known as niacin or nicotinic acid.

It is found in yeast, meat, tuna, seeds and vegetables. It is sometimes made from the enzyme tryptophan. It is involved in the DNA repair mechanism; cancer prevention; cell-signalling pathways and promotes apoptosis (cancer cell death). Its deficiency is linked to low lymphocyte (white immune cell) production and an increase in various cancers. Daily supplemental doses are up to 20mg.

Vitamin B7, more generally known as biotin, is generally taken as a component of a vitamin B complex. Its key role is in DNA repair. It is found in nuts, brown rice and whole grains.

Vitamin B9, more generally known as folic acid, plays an essential part in the correct copying of the cellular genetic code. It is found in melons, apricots, whole grains, avocados and many vegetables. Daily supplemental doses are up to 400mg.

Vitamin B12 is often deficient in vegetarians and people with low folic acid levels. It is an essential component in hundreds of chemical/ enzymatic reactions in the body. It is found in meats, seafood and chlorella. Most vegetarians supplement with chlorella.

Vitamin B17 is also known as laetrile (or amygdalin or hydrocyanic acid) and its use is somewhat controversial. The main source of vitamin B17 comes from the kernel of the apricot or similar stone fruits. The controversy involves the healthy form of organic cyanide in the kernel. Naysayers focus on the danger that the cyanide presents to the consumer of the vitamin. I recommend that any intended user fully acquaint themselves with the risks by consulting the literature before taking this vitamin.

A 1970’s book “Death of Cancer’ by Dr Manner details his research on laetrile, pancreatic enzymes, vitamin C, and vitamin A in his relatively successful treatment of cancer. His hypothesis that a deficiency in these enzymes brought about by their commitment to the digestion process of animal proteins (meats), contributes to tumour formation. This is the main reason to reduce meats in the diet.

There are large numbers of people who claimed to have cured their cancer by following a laetrile regime. Note that pure laetrile has been illegal in the USA for decades and is no longer sold in the UK.

Vitamin C is found in citrus fruits, broccoli, berries, red peppers, potatoes and tomatoes. The body does not produce this vitamin, nor does the body ‘hold’ more than about 7% of the vitamin ingested. It is a known immune system-booster, it protects the cells and cell walls from attack. (Vitamin C is effective against cancer cells through its support of immune system components like natural killer cells. It also benefits the functioning of neutrophils (bacteria killers), lymphocytes (antibody producers) and antibodies, which are all instrumental in the immune system’s ability to fight cancer cells and other illnesses).

When taken in large doses of greater than 25 grams it oxygenates cancer cells which leads to their death. It is a critical component in the fight against cancer. It is important to take it in a form that maximises its bioavailability to the cells. See the next chapter for Intravenous Vitamin C therapy.

Vitamin D has in recent years been the subject of a massive research effort. It is now clear that it is an excellent anti-cancer preventative agent (people with normal vitamin D levels have been reported as having a 50% lower incidence of cancer), and is a vital component in the fight against most cancers including prostate cancer. It is known that cancer cells have a large number of vitamin D receptors which makes them vulnerable to vitamin D attack. It is essential in signalling the body’s T-cells to attack rogue cells.

The good news about Vitamin D is that it is produced in the skin by exposure to sunlight for more than 30 minutes per day. It’s interesting to note that people living in the tropics have lower incidences of cancer (except skin cancers) than those in cooler (and less sunny or outdoor) climates. People who don’t get sufficient daylight exposure should supplement their Vitamin D intake in the form of vitamin D3 to levels around 6000 IU’s per day or higher. Note that a full summer’s day on the beach might provide as much as 40,000 IU’s. The only way to determine your vitamin D level is via a blood test. Ideally, your serum 25(OH) D level should be between 40 to 60 ng/ml year-round for optimal health and cancer prevention.

Vitamin E is available in two different biochemical formats, namely tocopherols (alpha, beta, gamma and delta) or tocotrienols, also in four forms. This vitamin has been subjected to extensive research in recent years. This research has revealed it as an important immune booster, it disrupts angiogenesis (blood cell growth) in tumours and has anti-metastasis properties. It is best taken in natural format by chewing seeds and nuts like sunflower, sesame and almond nuts/seeds. Alpha tocopherol succinate appears to be the most common format of Vitamin E used in supplements. Some industry participants see the four tocotrienols being more efficacious.

One should be mindful that the Selenium and Vitamin E Cancer Prevention (SELECT) trial reported in 2011 that there was a 17% increase in the incidence of prostate cancer in the vitamin E only participants. (Compared with the placebo group in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer). This study contradicts the findings of earlier studies which indicated reduced prostate cancer in men taking supplementary vitamin E. The participants in the study all took their vitamin E in the form of alpha tocopherol succinate only.

Vitamin K is thought to assist Vitamin D in their activation of the body’s T-cells in their fight against rogue cells. Various research studies have found

this vitamin to ‘stop’ some liver cancers as well as providing benefits to leukaemia and pancreatic cancer sufferers. Other studies have provided ‘inconclusive’ results.

Minerals

Potassium

The sodium-potassium balance of the body is all important in the control of the body’s pH value. We have heard that the body operates best when it has a pH value of 7.3 to 7.4 which sees it slightly alkaline. A person with an average diet is likely to see their sodium levels overwhelm their potassium levels. Potassium is essential to the internal mechanism of all human cells. The cell mitochondria use potassium in the energy production of ATP. Too much sodium in the body sees the sodium replace the potassium within the cell and lessens the cell’s energy production whilst turning the cell into an acidic environment. Any excess of sodium sees the kidneys expel potassium. An excess sodium concentration sees lower and lower energy output and an ideal environment for the birth of cancer cells. It also negatively affects the water balance of the body and adds to the stress, fatigue and ageing processes of the body.

It is critical to reduce the damaging sodium intake by limiting an intake of foods such as cheese, salt, bacon, nuggets, processed meats, white bread, sauces and gravy, soy products, French fries, salted peanuts, canned soups and salted butter and margarine. These are all high sodium foods. Also avoid Chinese and similar restaurant meals.

Foods high in potassium and low in sodium include potatoes, broad beans, lentils, bananas, green-leaf vegetables, nuts, brown rice, carrots and lean, organic meat.

Magnesium

Similar to the sodium-potassium balance in the body, is the calcium-magnesium balance. Too much dairy product in one’s diet, inhibits the body’s zinc, iron and magnesium uptakes. Magnesium is critical for the synthesis of Vitamin D in the body. Remember Vitamin D deficiency has been linked to the formation of a number of cancer types. It is also important to the efficient energy production by the mitochondria. Research shows that about 40% of Americans are deficient in magnesium. High levels of dairy intake also depress the magnesium levels in the body. Naturopathic doctors are inclined to recommend supplements to increase magnesium levels. Some recommend soaking in baths with magnesium chloride added whilst others are advocates of massaging magnesium oil into the skin.

Foods high in magnesium include melons, bananas, potatoes, nuts, sweet corn, green leaves and whole grains including brown rice. Dairy products should be limited or excluded.

Selenium

Selenium is an essential trace mineral that is found in most soils around the world. It is absorbed by plants and converted to mainly selenomethione or chelated selenium. It is used by cells in the body to defend against oxidative damage; to help maintain other antioxidants in the body (such as vitamin C and glutathione); to regulate thyroid hormone function and to stimulate the immune system.

Proponents of selenium suggest that these effects may explain its anti-cancer activity. The recommended dietary allowance (RDA) for selenium for both men and women is 55 micrograms (mcg) per day, but higher amounts are sometimes taken to lower the risk of cancer. The FDA warns that the daily intake of selenium should not exceed 400 mcg (1000 mcg = 1 milligram) unless supervised by a doctor. A typical Western diet might contain between 50 to 150 mcg per day. Adverse effects (including brittle hair and nails, skin rash, and neurological damage) have been observed in people taking more than 900 mcg per day. Foods rich in selenium include meats (liver and kidneys), fish, cereals and whole grains, poultry and Brazil nuts.

Selenium may be found in supplemental form as sodium selenite or L-selenomethionine. However, it should be noted that the Selenium and Vitamin E Cancer Prevention (SELECT) trial, which reported in 2011, found that in the placebo group 529 men developed prostate cancer, versus 575 men in the selenium group. More details are accessible via Appendix 3.

According to a study that was published in the Journal of the American Medical Association in December 1996, people who had taken selenium had 63% fewer prostate cancers, 58% fewer colorectal cancers, 46% fewer lung cancers and overall 37% fewer cancers.

Zinc

Zinc is an essential trace mineral in human nutrition and is the most abundant trace element in cells. The prostate is a zinc-accumulating, citrate-producing organ. The protein ZIP1 is responsible for the active transport of zinc into prostate cells. Zinc plays a key role in body processes such as building DNA and RNA, producing energy, regulating the immune system, and cell metabolism. It is an important antioxidant and a component of many DNA repair proteins and is considered to be especially important in the prostate, maybe protecting it from early damage that could lead to cancer.

The recent Health Professionals Follow-Up Study showed an increased risk of prostate cancer in men who consumed more than 100 mg daily. High-dose zinc has been shown to promote prostate cancer development. (Men on a ‘normal’ diet ingest an average of 11 mg per day). Converse to this, Dr Emily Ho at the Linus Pauling Research Institute, Oregon State University, reports that low zinc intake may increase the risk of prostate cancer.[9]

Many supplements are known to assist in the fight against cancer. However, the hard part is to take any supplement in the correct dosage and in the right matrix to optimise its efficacy. Recent research has identified prostate cancer as a ZIP1-deficient malignancy; which requires a mechanism or factor that will allow zinc uptake into the cell and its availability in the form of exchangeable reactive zinc. In vitro studies have demonstrated that the zinc ionophore, clioquinol, facilitates the uptake and accumulation of zinc which exhibits cytotoxic effects in ZIP1-deficient malignant cells. Clioquinol treatment is recommended together with the dopamine agonist, cabergoline, which decreases plasma prolactin levels, thereby preventing prolactin-induced progression of mCRPC. FDA ‘compassionate use’ policies permit the prompt availability of clioquinol and cabergoline treatment of terminal mCRPC.

Zinc inhibits NF-κB pathways, is anti-proliferative and induces apoptosis in abnormal cells. Unfortunately, oral ingestion of zinc is ineffective since high concentrations of zinc into prostate cells is not possible without the ZIP1 active transporter. Thus, the use of the clioquinol/cabergoline cream applied a number of times per day.

Zinc is found in seafood, meats, nuts, eggs, cheese, grains, and other foods.

Special Diets

The Southern Mediterranean diet

The Southern Mediterranean diet is high is fresh fruits and vegetables, olive oil, garlic, tomatoes, red wine, and fish. Red meat is seldom included. Dairy intake is also limited. Fish is included two or three times a week and should not be fried or burned during cooking. Nuts and herbs and cruciferous vegetables such as cabbage, broccoli and cauliflower are regularly included in this form of diet. In a study published online in the June 2013 "JAMA Internal Medicine" journal,[15] a team of researchers from the University of California, San Francisco, found that:

"A diet high in seeds, nuts, avocados, and oil-based dressing could reduce the risk of death for men with prostate cancer."

The research studied the fat intake of 4,577 men with non-metastatic prostate cancer over a 24-year period to 2010. It concluded that by replacing just 10% of their daily carbohydrates and animal fats with healthy vegetable fats, their prostate cancer mortality risk was reduced by 29%. The study, which was not a random controlled study, also suggested a 26% reduction in death from all causes, and called for further research to be undertaken on a healthy vegetable fat diet and prostate cancer.[11] Numerous research studies have been undertaken into the interaction of high vegetable fat diets and cardiovascular disease and/or prostate cancer. These studies suggest that there is increasing evidence that high animal fat and high carbohydrate intake may play a significant role in early prostate cancer formation.[12],[13] Research has suggested that the increased use of dietary micronutrients and antioxidants such as vitamins D and E, lycopene, selenium, zinc, isoflavonoids, and phytoestrogens (soy products and green tea) may offer therapeutic benefits against prostate cancer formation and subsequently to any existing prostate cancer.

Dr Myers' Diet

Dr Charles ‘Snuffy’ Myers was well known internationally as a prostate cancer specialist who has treated men from all corners of the globe. (Dr Myers is now retired). His great success was delivered by adherence to his three key tenets: Extensive Research, Cutting Edge Assessment and Personalised Care. He was of the view that nutrition and lifestyle are vital components in the prevention and treatment of prostate cancer. This belief saw him introduce an improved and updated edition of his earlier successful book “Eating your Way to Better Health” which has been re-named “The New Prostate Cancer Nutrition Book.” To quote from his web site accessible via Appendix 3.

“Using indisputable research on the health-benefits of the Mediterranean Diet, this new edition tackles the most pertinent issues in the field today with evidence-based analysis.”

Perhaps, an observation of interest is that the cover of his book shows the following:

Avocado, tomato, onion, broccoli, beans, pomegranate, cherry, Kiwi fruit, garlic cloves and various nuts.

The Japanese Diet

Prostate cancer in Japanese men is at a significantly lower level than in those with a Western diet.[14],[15] Their diet is high in fish, soy and vegetables. It is low in calories (meat) and fat. Green tea is also an important component of most meals.

The Rainbow Diet

Over the last year or so, I have bought and encouraged others to buy and read a copy of Chris Woollams's book "The Rainbow Diet – And how it can help you beat cancer." Of course, it's not enough just to read the book. It is necessary to read it, understand it and ACT on the great advice contained within its 347 pages. Most of my friends are now in the 60 to 75-year age bracket: the age span when things start to go wrong with our bodies, due to us abusing our mind and body for perhaps 50 years or more. It is time to pay more attention to our ongoing health and dietary needs.

The book is very comprehensive and hopefully, many of my friends (and an occasional relative) have started to heed its key message. The book's key premise is:

Get the bad guys out of your diet; improve the purity of your tap water; eat organic foods; stop packaged, fast and microwaved foods; eat more herbs and spices; eat five or six small, but nutritious meals a day; oxygenate your body via exercise; supplement with quality vitamins and minerals; keep your body alkaline; maintain much of the goodness in the food by taking it raw; take daily doses of sunshine (or supplement with vitamin D), but above all put colour into your diet by consuming a spectrum of red, orange, yellow, green, purple/blue and white/brown vegetables and fruits.

Chris Woollams has written this book to get people to understand how we have ignored the foods and natural compounds that have protected us for the last 200,000 years. He runs a cancer charity in the UK called CANCERactive and also publishes the ICON magazine that is available to cancer patients in UK hospitals. His web site, accessed via Appendix 3, is one of the most comprehensive cancer sites in the world. One of his other books is titled "Everything you need to know to help you Beat Cancer." As it says on the front cover: "Easy-to-read; the most comprehensive anti-cancer book available." I fully concur.

Fasting

To successfully fight cancer or to keep it away, the immune system must be maintained in as good a shape as is possible. In this book, you will find details as to how to optimise the immune system. An increasing number of health professionals believe that fasting offers a quick turbocharge of the immune system.

Recent research has suggested that fasting for as little as three days can regenerate the entire immune system, even in the elderly. Of course, many nutritionists still believe that fasting diets are unhealthy. The new research might be changing their minds somewhat when they realise that starving the body, kick-starts stem cells into producing new white blood cells, which fight off infection.

Other General Dietary Comments

Pomegranate juice was found in a 2006 UCLA research study to slow or even reverse the recurrent cancer rise in PSA after initial treatment. The men's overall PSA doubling time was nearly four times slower after they drank a glass of pomegranate juice (8 fluid ounces. or 250ml) every day for 33 months. Sixteen of the 46 patients had a decrease in PSA levels. In four participants their PSA levels dropped by half.[16] The US National Cancer Institute’s web site covers the issue of pomegranate juice extensively. Access it via Appendix 3.

What to Do about Diet, Nutrition and Supplements

Two doctors and my late brother on reading this draft all suggested that I should draw conclusions from all what has been included in this chapter. I suspected that one of the doctors wanted to see what I had recommended. I take this as something of a complement. I have decided to wimp out on compiling detailed recommendations as I do not believe that it is my role to do so, considering the importance of the issue. So, what I will do is to tell you what I strive to do to try to avoid or reduces the possibility of a recurrence of my prostate cancer. I will also tell you what a friend who has CRPC is doing to rid himself of the disease.

My Diet and Supplementation

Bear in mind that my prostate cancer is in remission. Therefore, my diet is one to hopefully minimize the chance of its recurrence.

Breakfast

Wholemeal toast spread with unrefined coconut oil and a light spread of marmalade.

A bowl of eight fresh fruits including: strawberries; blueberries; raspberries; kiwi fruit; watermelon; rock melon (cantaloupe); banana; red grapes.

A small serving of quality yoghurt which has no added sugar has recently been included.

Lunch

Usually a salad containing half an avocado, lettuce, red and green capsicum; tomatoes, red onion, cucumber, celery, radish, cold range feed chicken with minimal olive oil-based dressing. A couple of times a week, I break the rules by substituting the chicken with ham. Twice a week, I have two bananas only.

Dinner

Two glasses of red wine (for their resveratrol content!).

Lightly steamed vegetables: carrots; Brussel sprouts; broccoli, brown rice; peas; potatoes; pumpkin; mushrooms; onions; etc. Occasionally, cauliflower; cabbage and stringed beans.

Grilled fish (once a week); steamed chicken; grilled loin chops; mutton curry with curcumin; occasionally grilled pork chops; mince beef; etc.

Small desert (minimising dairy and sugar)

Coffee with minimal milk and with Stevia sweetener.

I try not to eat anything after 8pm, which sees me fasting for 12 hours, during which period the body relies on body fat to provide it with its nutritional requirements.

I am very conscious of the contents of all food purchased. I avoid foods with trans-fats, too high sodium and sugar content. Also processed and ‘instant’ microwave meals.

Supplements

I take a daily multivitamin and mineral tablet; vitamin D3 (1500 IU); magnesium (300mg); calcium (25mg); flaxseed oil (1000mg); selenium (150mcg); vitamin C (1000mg); lysine (1000mg); krill oil (1000mg) and alpha lipoic acid (200mg).

My Friend’s Diet and Supplementation

I met Fred at a Prostate Support Group a few years ago. He had not long before been diagnosed with mCRPC with a few bone spots in the pelvic area and a couple more in the lower spine and a rib. His PSA has dropped from over 100 when diagnosed to single digits after initial ADT and more recently enzalutamide. After contact with the usual conventional specialists he had a consultation with an integrative medical specialist and adopted her dietary recommendations. He said why not attack the cancer from both conventional and alternative directions. Of course, it is important to check that the supplements don’t interact with conventional treatment.

Throughout the Day

He uses only filtered water produced by his reverse osmosis water purifier. He enjoys at least 6 cups of green tea per day. (He is considering changing to the Essiac tea mixture). In the morning and before retiring to bed he has a glass of water to which he adds a teaspoonful of sodium bicarbonate to help alkalize the body. He occasionally substitutes a glass of organic apple cider vinegar instead of the bicarb solution. He nibbles on unsalted fresh nuts (almonds, cashews, walnuts, etc.) throughout the day and evening.

Breakfast

His breakfast consists of two main components, namely flaxseed oil with cottage cheese (FOCC – about 250ml.) and sometime later a bowl of in-season fruits (berries, pomegranates, red grapes, papaya, melon, etc.). Sometimes lemon juice is squeezed over the fruit offering. The FOCC is freshly prepared daily and allowed to stand for 20 minutes before consumption.

Mid-morning

He has up to 100ml Bravo yogurt GcMAF (at least 90 minutes after his morning vitamin D). This product contains a massive 42 different bacteria and yeast strains. The preparation of this product sees the inclusion of several powerful bio-active molecules such as lactoferrins, immunoglobulins, antioxidants, vitamins and the very powerful immune-stimulating factor called GcMAF which assists in restoring a healthy gut microbiome.

Lunch

A number of days a week, a salad similar to the salad I have which contains some veggies like avocado, lettuce, red and green capsicum; tomatoes, red onion, cucumber, celery, radish, with minimal olive oil-based dressing. From time to time, he has a canned fish on brown rice or a little chicken, but no red meat. A couple of times a week he has home-made vegetable soup with a slice of ancient grain bread.

Dinner

Baked or steamed potatoes (no mash with milk); peas, beans and other lentils; cooked tomato; a cruciferous vegetable (broccoli, cauliflower, sprouts, etc.); garlic; spinach; squash; onions; poached or boiled organic eggs; deep sea oily fish; vegetable curries with turmeric, ginger and other herbs added; unrefined brown rice; a variety of mushrooms. Occasionally a small serving of free-range chicken.

He didn’t comment on any desert that he might take regularly or occasionally.

Supplements

Vitamin D3 (5000 IU); vitamin K2 (180mcg); magnesium (300mg); vitamin C (up to 10gm); grape seed extract (12000mg); selenium (180mcg); zinc (15mg); astragalus (2000mg); krill oil (1000mg) and a vitamin B complex.

Chapter 21.

Alternative Therapies

In this section of the book, we look at alternative therapies that are not mainstream treatments and may never become ‘approved’ treatments by the medical establishment supported by their governmental authorities.

At the outset and to give an extreme example, blood-letting was considered standard practice as recently as the 18th century. It is likely that some alternative treatments available today will over time join the mainstream and become ‘approved’ treatments. The tragedy of this is that there are thousands of cancer sufferers alive today who have been told that conventional medicine cannot do any more for them. As a regular speaker at Prostate Cancer Support Groups in Australia, I meet such men on a regular basis. This circumstance has been the main driver in me producing this third edition book, which might offer this large group of sufferers a path forward.

As has been outlined earlier in the book, there are four main components of a sufferer’s plan to fight their cancer. These are exercise; diet and nutrition, peace of mind and finally, the treatment protocol. We have addressed ‘peace of mind’, ‘exercise’. We have addressed all the major conventional medical treatments for prostate cancer and addressed ‘diet and nutrition’ in the last chapter. It’s time to look at alternative treatments. These will include sonophotodynamic therapy; ozone, hydrogen peroxide and hyperbaric oxygen treatments; intravenous vitamin C ‘dosing’ and combo treatments at clinics that are registered and sited outside, for example, the USA. These treatments are considered below in no particular order of priority or importance.

However, before considering the possible suitability of any or all of these treatments for yourself or a friend or family member, please bear in mind that I am not a doctor and am not qualified to give medical advice. What follows is NOT medical advice, but rather a brief summary of some treatments that have been found to yield beneficial outcomes in some people. Remember what works for one individual might not work for another person and may result in negative and serious outcomes. Please review the health warnings earlier in this book and always consult an appropriately qualified medical practitioner before embarking on any of the treatment regimes outlined in this chapter.

Please recognise that many medical practitioners have had limited or no exposure to diet, nutrition or alternative therapies. It may be beneficial to search out an integrative medicine professional experienced in both ‘conventional’ and ‘alternative’ medicine.

Sonophotodynamic therapy (SPDT)

The first edition of this book was completed in November 2013. At that time PDT or Photodynamic Therapy was referred to only in the glossary of the book. Since that time the technology has advanced further with a greater uptake of its usage. The technology has seen sensitisers developed that respond to both light and ultrasonic energy, thus combining the two capabilities of PDT and SDT (sonic dynamic therapy). PDT has been around for many years for the treatment of surface or near surface cancers and cancers that can be reached by using a fibre-optic cable for the delivery of the light needed to activate the sensitizer. Skin, lung and oesophageal cancer are commonly treated by PDT.

PDT, SDT and SPDT all use a sensitising drug that migrates preferentially to all cancer cells over a 24 hour or longer time frame. This sensitiser is activated by light (PDT), ultrasound (SPT) or a combination of both (SPDT). The energy released breaks molecular oxygen into singlet oxygen and free radicals which cause damage to the cancer cells, and leads to cancer cell death (necrosis). The treatment generally has few side effects. SPT and SPDT are used for deep-seated cancers like prostate cancer and is often used in conjunction with one or more other cancer therapies such as whole-body hyperthermia, etc.

Exercise with Oxygen, Ozone, Hydrogen Peroxide and Hyperbaric Oxygen Therapies

Dr Otto Warburg, a German biochemist, was awarded the Nobel Prize for medicine in 1933, for his discovery of the role of oxygen in cancer cell physiology. He said at the time;

"Cancer has only one prime cause. The prime cause of cancer is the replacement of normal oxygen respiration of body cells by an anaerobic (oxygen-less) cell respiration."

Cancer cells exist in an oxygen-less environment. To create the necessary energy to grow they resort to a process called fermentation. This inefficient process produces only about 7% of the energy output of a healthy cell. The cancerous cell has a huge appetite for glucose and other sugars to feed the fermentation process. Normal cells give off carbon dioxide (CO2) during the respiration process whereas cancer cells give off lactic acid. This release of CO2 assists the blood's haemoglobin to transfer oxygen throughout the body. Lactic acid impedes this process.

There are many reasons why healthy cells become starved of oxygen and become cancerous. What is important is that the body is 'fully oxygenated' all the time to prevent healthy cells becoming cancerous and to kill cancerous cells by saturating them with oxygen, which leads to their death or repair back to healthy cells.

Oxygen therapies are considered with suspicion by the medical authorities in many countries, but are an essential weapon in the doctor’s toolkit in Germany. There it is considered an important aid in removing the underlying cause of various diseases including cancer.

Exercise with Oxygen Therapy (EWOT)

This very simple therapy was first reported by Dr Manfred von Ardenne, a German physicist. He hypothesised that any type of stress on the body resulted in a decreased level of oxygen absorbed into the blood. In turn, this decreased oxygen in the body’s tissues has subsequently been found from research to foster the start and growth of cancer cells.

EWOT consists of doing light exercise, such as on a stationary bicycle or a treadmill, while breathing pure oxygen. EWOT helps to increase the oxygen level in the venous blood, blood plasma and tissues. Venous blood is normally the colour of red wine whilst fully-oxygenated blood is bright scarlet.

After 10 to 20 minutes of EWOT (dependent on the exercise rate and oxygen flow), a patient’s skin often begins to redden, which is known as ‘pinking up.’ This phenomenon is a result of the increased oxygenation of the cells of the body. The oxygen is delivered by a medical grade oxygen cylinder supply or an oxygen generator. This procedure should be directed by a medical professional experienced in oxygen therapies as there are inherent dangers in ‘over-oxygenating’ the lungs.

Ozone Therapy

We have all heard of the ozone zone in the upper atmosphere. It consists of ozone atoms that are similar to oxygen atoms, but have a third oxygen atom, compared to oxygen's two atoms. The ozone protects us from the harmful UV radiation coming from the sun. Ozone is also a well-known sterilizing agent and as a cancer-fighting agent.

Dr Frank Shallenberger, a proponent of ozone therapy, has clearly enunciated the difference between ozone and oxygen therapies and why ozone is specifically preferred as a treatment for cancer. It all revolves around the effect use of oxygen by the mitochondria of the healthy cell. Ozone delivery sees the oxygen used far more efficiently by the mitochondria ATP energy production.

Healthy cells, receiving the necessary supply of oxygen, produce an enzymatic coating around the cell. This protective layer prevents bacteria and viruses from invading the cell. The protective layer includes the enzymes catalase, superoxide dismutase, glutathione peroxidase, and reductase.

The protective layer around oxygen-deprived cells is undeveloped which sees the cells susceptible to attack by toxins and other 'nasties'. These invaders compromise the mechanisms of the healthy cells and quickly converts them into rogue cells which replicate uncontrollably.

Unlike oxygen, ozone selectively kills cancer cells. The absence of the enzymatic coating, allows the ozone to penetrate the rogue cells and cause the death of the pathogenic material within the cell. Ozone atoms are electrically unstable. This instability attracts them to pathogens which sees them ensure the cell's death. Pure oxygen does not do this in quite the same way, but both ozone and oxygen kill viruses, the likely cause of many cancers.

There are more than a dozen ways of administering ozone therapy. The two most popular both require the services of an experienced intravenous (IV) practitioner. In autohemotherapy, medical grade ozone is infused directly into the vein or blood is withdraw from the body, treated with medical grade ozone and then returned to the body. Alternatively, the medical ozone gas could also be mixed with a saline solution and injected venously into the body, again by using an experienced intravenous practitioner or qualified medical professional who is fully experienced in this therapy.

Another popular treatment method is transdermal absorption by the use of a sauna tent, ensuring that ozone is not vented to the exposed head area of the patient that is external of the tent. This treatment is available at many health clinics. Another method is self-administration which is done by using a technique called insufflation, where the medical grade ozone is introduced to the rectum via a catheter. The rectum should be cleared before this treatment.

It has been found beneficial to take a series of antioxidants at least two hours prior to each ozone treatment session. These include vitamins C, A, and E, and pycnogenol or grape seed extract. Some people repeat the dosage after the treatment concludes.

Some patients' experience discomfort from their treatment with ozone. This is caused by the detoxification reaction in the body. Symptoms may include flu-like joint pain, body aches, sweating, or nausea which may last only a few hours or much longer. Some cases have felt one or more of these symptoms for up to two weeks after the last treatment. A throat irritation, resulting in a coughing spree on occasion, suggests that enough ozone has been ingested. A paper by Jane G. Goldberg gives an excellent commentary on ozone therapy. It is accessible via Appendix 3.

In a book titled “Flood Your Body with Oxygen” written by Ed McCabe, he outlines his preferred ozonation process that he called ‘Extracorporeal

Recirculatory Hemoperfusion' (RHP) or 'Polyatomic Apheresis'. Pure molecular oxygen is used as the primary carrier with the ozone added to it. The mixture is administered via a sophisticated dialysis-type system that sees the blood withdrawn from the patient, immediately exposed to the oxygen-ozone gas, filtered and returned in fully oxygenated form to the bloodstream. A pile of pale powdery substance is left in the clear glass perfusion bowl. This substance consists of dead cells, toxins, microbes and other garbage in the blood. McCabe suggests in the book that significant results are achieved by RHP within 'just weeks' rather than the usual six months or longer for other less efficient ozone methods. Daily or every other day treatments typically last for 45 to 60 minutes initially, increasing to up to three hours per session. In addition to removing the 'nasties' from the blood, it eventually perfuses into all body tissues, including the bones.

Hydrogen Peroxide

We have all been exposed to hydrogen peroxide (H2O2) at one time or other, particularly as a household disinfectant. Surprisingly, human white blood cells make hydrogen peroxide themselves, and do so to oxidize and fend off invading bacteria and viruses.

A few friends of mine, who are now in remission from cancer, have tinkered with H2O2 treatments as simple as placing a few drops in their soaking baths. Here, I discuss a specific H2O2 program which should be administered and regulated by a medical practitioner. The doctor will consider the patient's individual circumstances such as the severity of the cancer, body weight and sensitivity to the remedy in preparing a treatment regime. Administration is through IV therapy or orally.

Since Dr Charles Farr was nominated for the 1993 Nobel Prize in medicine for his research in the therapeutic use of hydrogen peroxide, it has generally been dismissed as a cancer treatment in North America, but is still used in Europe and elsewhere.

Hyperbaric Oxygen Therapy (HBOT)

A golfing friend of mine whose brother-in-law (Jim) has metastatic prostate cancer asked me recently what I thought of hyperbaric oxygen therapy. Apparently with chemo not providing sustainable benefits, Jim’s medical team judged that he might benefit from a series of exposures to hyperbaric oxygen. Jim’s treatment saw him exposed to a 100% pure oxygen environment at twice normal atmospheric pressure for four hours three times a week for three weeks. He was advised the purpose of the treatment was to stimulate the body’s immune system to attack the cancer. Outcome: Inconclusive to date.

HBOT and EWOT are considered not to be as effective as are ozone and/or hydrogen peroxide therapies, as oxygen, even under pressure, is not a strong enough oxidizing agent as is hydrogen peroxide and ozone. Ozone being the stronger oxidizer of the two. Remember that the enzymatic protective coating of cancer cells is non-existent or is under-developed, thus exposing them to the killing power of strong oxidizing agents like ozone and hydrogen peroxide.

Intravenous Vitamin C (IVC)

Vitamin C (ascorbic acid) has been considered a powerful antioxidant for many years. It is water-soluble and is involved in many biological functions. It is sometimes referred to as ascorbate, or IAA (intravenous ascorbic acid) treatment. It also has the ability to act as a detoxifier by being able to oxidise tissue in a similar manner to chemotherapy.

It is involved in maintaining proper immune cell functionality. The natural killer (NK) cells of the immune system require high levels of vitamin C to operate effectively. It assists in the production of antibodies and has the ability of lessening the spread of tumour cells to adjacent healthy tissue. Vitamin C also boosts the body's production of interferon which has anti-cancer activity.

Another benefit is provided when IVC-dosed patients undergo radiotherapy. It has been reported that they suffered less anaemia, less pain, and less loss of appetite and weight if they were given vitamin C concurrently with the radiotherapy.

A very important role that vitamin C plays in the body's fight against cancer is in its ability to form a complex with food iron which increases its bioavailability and uptake. (Most cancer patients suffer from an iron deficiency). The resultant increase in blood haemoglobin assists in the oxidative energy function of cells.

The body will only absorb a limited quantity of vitamin C when it is taken orally. It is also known that when taken intravenously, the absorption rate increases by as much as 100 times that of orally-taken vitamin C. In a 2004 study by the NIH, the blood concentration of vitamin C when given intravenously was nearly 7 times greater than when the same amount was given orally. And the maximum tolerated dose was nearly 20 times higher.

Linus Pauling, PhD (who won two Nobel prizes in 1954 and 1962) cooperated with medical doctor Ewan Cameron to treat a large series of terminally ill patients with 10 grams per day of IVC about 40 years ago. Simultaneously, other patients with similar progressions of their cancer continued conventional treatment without IVC. Over time Dr Cameron added other vitamins and minerals to their IVC protocol. When interviewed in 1996, Pauling said:

“Cameron’s terminal cancer patients lived far longer compared to the ones who didn’t get 10 grams per day of vitamin C. The other patients lived an average of six months after they were pronounced terminal, while Cameron’s patients lived an average of about six years.”

Numerous clinics around the world have offered an even higher dose IVC treatment for many years with meaningful results when measured by patient longevity. These include patients with prostate cancer. Of course, as is always the case, some patients fared far better than others.

One such clinic is the Dove Clinic, Hampshire, UK, which is run by Dr Julian Kenyon. He outlined their protocol recently in an interview with Dr Chris Woollams of CANCERactive UK:

“Plasma levels of vitamin C between 300-400 milligrams per 100 cc are required in order to kill significant numbers of cancer cells. This requires intravenous infusions of 75 grams of vitamin C, (in some cases less, depending on the size of the patient and the tumour cell mass), infused intravenously on a daily basis for three weeks in order to be able to attain these plasma levels.”

In 2011, the FDA ruled that all US clinics should stop IVC treatment immediately as it was being used ´as a drug´ and therefore needed FDA approval, which would only be forthcoming after successful clinical trials. ‘Big Pharma’ would not fund such trials as vitamin C is a natural compound and is therefore not patentable. However, it is pleasing to note that a number of clinical trials are underway at this time to establish the efficacy of IVC together with a drug and/or radiation. None of these trials covers prostate cancer. It is pleasing to see IVC therapy continuing in many countries.

So how does IVC work? Several studies have shown that vitamin C administered by IVC, has a direct cytotoxic effect on various types of cancer cells via a chemical reaction that generates hydrogen peroxide (H2O2). Cell death occurs in cancer cells exposed to high levels of oxygen provided by the H2O2. Another study suggested that ascorbate-mediated prostate cancer cell death may occur through activation of an autophagy (regulated self-destruction) pathway.

For those not willing to adopt IVC, there are many advocates for a lesser vitamin C protocol espoused in the 80’s by Dr Linus Pauling and his fellow researcher, Dr Matthias Rath. They recommended daily doses of a vitamin C mixture to which was added two common amino acids, namely l-Lysine and l-Proline. (A commercial product called Heart Plus is available in the USA from ‘Our Health Coop'). They subsequently found that adding a green tea extract to the mixture further improved its anti-metastatic properties.

Another variant of IVC sees a drug, normally used to fight serious bouts of malaria, called artesunate, infused immediately prior to an IVC session. It is known that cancer cells absorb iron at high levels and this is thought to accelerate the mutation rate within these cells. Artesunate reacts with the high iron content in the cancer cells to kill the cancer cells. Research suggests that a better anti-cancer result is obtained when the high dose intravenous vitamin C follows intravenous artesunate. Artesunate is synthesised from the common garden plant artemesia, or wormwood. Artemisinin is another derivative and has been used for thousands of years to treat various cancers.

Some medical scientists suggested that liposome-encapsulated vitamin C, taken orally, presents a higher bioavailability of vitamin C to the body’s cells, than even with high doses of IVC. Liposomes are most often composed of phospholipids, (especially phosphatidylcholine), which form a biolayer around the active agent, in this case, vitamin C. Dr Thomas E. Levy, the author of numerous books, including “Curing the Incurable”, “Death by Calcium” and “The Toxic Tooth”, advocates a multi-vitamin C protocol. This includes:

Firstly, a liposome-encapsulated vitamin C, 1 to 5 grams taken orally daily (not homemade formulations). Secondly, sodium ascorbate taken daily up to or reaching bowel tolerance (C-flush). Thirdly, ascorbyl palmitate, 1 to 3 grams taken orally each day. Finally, intravenous vitamin C (sodium ascorbate or buffered ascorbic acid), 25 to 150 grams, depending on body size. (Sometimes daily initially, and often several times weekly to monthly depending upon clinical circumstances). More details at Appendix 3.

See the section on mitochondrial inhibitors in Chapter 14 which discusses the use of IVC with doxycycline.

The Budwig Diet (Flaxseed Oil and Cottage Cheese)

Dr Johanna Budwig, a German biochemist, who came to prominence in the 1950’s, was a truly remarkable woman, being nominated for not one, but seven Nobel Prizes during her lifetime. She was a prominent researcher in the field of vegetable oils and fats and was the first to establish that essential polyunsaturated fatty acids, are major components of cellular membranes. She found that without a properly functioning cellular membrane, cells lose the ability to perform vital life processes such as cellular respiration and the ability to divide and form new cells. These essential polyunsaturated fatty acids are known today as omega-3 and omega-6 fatty acids or linolenic or linoleic acids.

Dr Budwig believed that cancer has three causes:

A virus and/or fungus enters healthy cells;

Toxins weaken the cells and enable the virus to enter healthy cell;

Finally, nutritional deficiency.

Dr Budwig found that the right combination of quark or cottage cheese and flaxseed oil had strong therapeutic properties in preventing, treating, and even curing cancer. When mixed in the appropriate way, these components complement each other to form a strong anti-cancer treatment over a wide spectrum of cancers including prostate cancer. She is said to have successfully treated more than 2000 cancer sufferers up until her death at age 93.

Over the past few years, a number of scientific papers have been published that have concluded that too high a consumption of omega-3 fatty acids were likely to contribute to the growth of prostate cancer. Most of these studies refer to omega-3 oil ingestion and not the flaxseed oil with cottage cheese (FOCC) mixture. Two studies did look into the impact of FOCC and prostate cancer. All these studies were epidemiological in nature which means that they can tell us about the relationships between things, but not that one thing is causing another.

The highest profile study was led by Theodore Brasky, PhD, of the Fred Hutchinson Cancer Research Centre in Seattle, USA and published in the Journal of the National Cancer Institute in July 2013. Prostate cancer expert Anthony Victor D'Amico, MD, PhD, commented on the study findings:

"The study really cannot make the conclusion that it's trying to. These types of studies are not cause and effect. These studies are simply associations. They didn't account for the known predictors of prostate cancer when they were making the calculation. You're left with a weak association."

The Budwig diet is followed by tens of thousands of cancer sufferers worldwide, with apparently significant success. It is thus important to determine the likely significance or impact of this study on existing or potential users of high-level doses of omega-3 oils. See Appendix 3 for a detailed rebuttal of its findings which you might find enlightening. To be fair I have a problem with some of the rebuttal arguments. One of the studies covering FOCC use, reached conclusions that to me, directly contradicted core data included in the study.

Two final points on FOCC use. Firstly, it should be all consumed within 20 minutes of it being prepared and it should be produced in exactly the time outlined. If both these conditions are not met, its efficacy is significantly reduced. The second point is that those on the FOCC diet should reduce their antioxidant intake whilst on the FOCC diet according to the Budwig Clinic in Malaga, Spain. My analysis of the diet of six or seven men on this diet sees them all taking a number of antioxidants every day which may reduce the efficacy of the FOCC regime.

The Gerson Therapy

It was established more than seventy-five years ago by Dr Max Gerson, and it is fully described in his book: “A Cancer Therapy: Results of Fifty Cases and the Cure of Advanced Cancer.”

The Gerson Therapy calls for the daily ingestion of natural products in juice form, which are designed to heal the body against cancer, heart disease, and other illnesses. The detoxification of the body and the addition of supplements completes the treatment regime.

Gerson Therapy requires that up to thirteen glasses of fresh, organic juices (fruit and vegetables) be consumed daily. The objective is to provide the body with extreme doses of enzymes, minerals, and other nutrients. This gives the body the ability to break down and eradicate diseased body tissues.

The juice routine is complemented by three vegetarian meals with fresh fruit each day. Organic supplements such as vitamin B12, pancreatic enzymes, potassium and iodine are amongst those included in the daily diet.

Dr Gerson believed that an imbalance between typically high sodium levels and too low potassium levels contribute to the formation of cancer. The diet prohibits all processed foods, nuts, berries and anything that contains sodium. The use of aluminium cooking utensils is also unacceptable.

Inpatients at the Gerson Institute run by Dr Gerson’s daughter in the USA, have multiple coffee enemas each day to purge the toxins from the liver and other organs. Some additionally have ozone therapy and other enema types to clear the system of their ‘nasties’. The Gerson Institute claims to ‘cure half of the patients who have a month to live, and 90% of patients with any early cancer’. There are various clinics in Spain, Germany, Mexico and elsewhere, who precisely follow the original Gerson Therapy or variants of the same.

Far InfraRed Light or Heat Therapy

It has been known for many hundreds of years that fevers are nature’s way of repairing the body. It has been known for less time that low body temperature slows the immune system’s response, whilst higher temperatures activate the immune system’s response to threats. As explained in the chapter on hyperthermia earlier in the book, cancer cells cannot stand being exposed to temperatures of between 39° C (102° F) and 48° C (118° F) for more than an hour on a number of occasions. Under the section on whole body hyperthermia in that chapter, I discuss the use of far infrared saunas which have a maximum practical in situ temperature of 42° C (108° F). I refer to WBH as being often a treatment of last resort as it is used in the majority of cases on patients with metastatic lesions external of the prostate region. It is beneficial to the patient to reduce the size and distribution of the metastatic cancers whilst undergoing a primary treatment.

A product that is in reasonably widespread use for this purpose individually and in private cancer clinics around the world is the Bio-Mat®. This product has been used by astronauts on the NASA space program and uses targeted infrared heat therapy to boost the delivery of oxygen-rich blood to the muscles, thus alleviating pains, stress, inflammation, sleeping disorders and immune issues. At its highest temperature settings, its heating effect radiates into the body to a depth of about 150mm.

The product has three active ‘components’. Firstly, two of the seventeen layers of the Bio-Mat consist of tourmaline stone which is a natural emitter of negative ions. Secondly, other layers contain amethyst crystals which over many centuries has become known as a power crystal with prolific healing powers. It radiates 10 to 12 micron wavelength far infrared radiation into the person in contact with the mat. Thirdly, this energy is adjustable via a controller. Note that the radiated far infrared energy converts into heat energy within the body.

It all sounds like quackery, but tens of thousands of people use them daily and are very vocal in their support of its efficacy. Some number of Bio-Mat users with prostate cancer have found its use ‘beneficial’. (A claim NOT made by the manufacturer).

Some infrared devices resemble the design of more conventional saunas, in that the patient is ‘boxed’ in the device. Some brands offer infrared heating at three wavelengths which are selectable. An important consideration in selecting an appropriate device is to determine their electromagnetic field (emf) output. This should be as low as possible.

Combination Therapies at various Cancer Clinics

I was invited to attend a regional prostate cancer conference a year or so ago. Unfortunately, I couldn’t make it due to a prior commitment. I sent them a few complementary copies of my book as a lucky seat prize. When buying a satchel at the post office to send these books, a woman came over to me and said: “I hope you sell lots of your book as we need to make men far more aware of the dangers of prostate cancer. You see my husband died recently from prostate cancer.” Continuing to chat, she told me how her husband’s doctors had given up on treating him, other than providing palliative care. I have seen numerous cases going down this same path at prostate support group meetings. Men essentially without hope.

I have also interviewed men who have tried alternative treatments with success or have attended overseas clinics which have offered combination therapies, which have also provided good outcomes. Conversely, Big Pharma in some ‘advanced’ countries have contributed to the road-blocking of some treatments that would likely have provided satisfactory or better outcomes in clinical trials. National health authorities and medical associations find it too easy to maintain the status quo, thus making it more difficult for needy patients to access lifesaving treatments.

In 2017 I read a book titled “German Cancer Breakthroughs – A Guide to Top Clinics” by Andrew Scholberg. 3rd Edition - Published in 2017, it reviewed the treatments available at that time from the following German clinics:

Hufeland Klinik in Bad Mergentheim

Fachklinikin Bad Salzhausen

BioMed Klinik in Bad Bergzabern

Dr Ursula Jacob’s Privatklinikin the Black Forest

Praxisklinik in Bad Aibling

St. Georg Klinik in Bad Aibling

Klinik Marinus am Stein in Brannenburg

Gisunt Klinik in Zetel

One of these clinics was quoted to say: “There are no untreatable patients.” You might recall that I seriously considered going to the St. Georg Klinik for transurethral hyperthermia treatment. Treatments that are provided at all these clinics are: Hyperthermia (whole body, local and transurethral); IV vitamin C (with selenium in some cases); magnetic field therapy; immune system boosters; oxygen and ozone therapy; colonic detoxification; alkalising diets, and insulin potentiation therapy. Individual clinics offer additional therapies such as blood laser therapy (based on NASA research); mistletoe; galvano-therapy; live cell therapy; laetrile; Budwig (flaxseed oil and cottage cheese); lactic acid; dendritic cell; homeopathy; thymus peptides and fever by injection. These clinics have documented success stories for their treatment of many, many prostate cancer sufferers.

An interesting fact emerged about patients attending these clinics from the USA and their health insurance coverage. Apparently, the American Medical Health Alliance facilitates successful insurance claims for up to 85-90% of the costs incurred.

I have had family reasons to evaluate cancer treatment clinics in other countries in Mexico, Spain and Japan. Two leading clinics based just south of the US-Mexican border in Tijuana are the Dr Jimenez's Hope 4 Cancer Institute and Dr Vickers' Advanced Gerson Clinic. Dr Vickers' clinic offers the Gerson Therapy as well as many of the therapies offered at the German and Swiss clinics listed above. Dr Jimenez has opened a second clinic in Cancun, Mexico which is more accessible to potential patients from the US East Coast.

Other Alternative Therapies

The more one digs into the search for alternative therapies to fight prostate cancer and to evaluate their likely efficacy, the more treatments emerge. There are literally hundreds of treatments that have yielded little or no success, good success or even better than that. I have looked in detail at many of them. Some are more appropriate for cancer types other than prostate cancer, whilst others appear to 'work' across a range of cancer types including prostate cancer.

The purpose of this book, other than to report on "My Journey over Four Continents to Find the Best Cure" for my prostate cancer, is to present a comprehensive picture of what diagnostics, treatments and therapies are available to a newly-diagnosed prostate cancer sufferer and his family. It would be remiss of me not to include a range of alternative treatments that might assist those with metastatic cancer, who have perhaps been 'forgotten' by mainstream medicine.

I have included information on a series of alternative therapies that might have an understandable basis of science behind them. Bear in mind that I am NOT a medical doctor and am NOT giving medical advice. Anyone considering adopting any of the protocols, should only do so after full dialogue with their medical team and full consideration that it is their responsibility and their's alone, should they embark on such treatment. The author cannot be held responsible for any action, or lack of action, that is taken by any person as a result of information contained in the text of this book.

A few years ago, I read the book "The Complete Guide to Alternative Cancer Treatments" published by Online Publishing & Marketing, LLC. It covers more than 340 treatments over its 470 pages including entries under the following categories: Diet; herbal; plant-based; greens; mushrooms/ yeasts; marine; animal/insect; immune; vitamins/natural products; minerals; oxygen; alkalising; enzymes; Chinese; Ayurvedic; urine; topical; alternative treatments; mental/emotional; exercise; drugs and detox/antimicrobial/antiparasite. More details are accessible via Appendix 3.

In 2015 I had the privilege of being exposed to Ty Bollinger's "The Truth about Cancer – A Global Quest." This was a series of 9 videos that ran for more than 13 hours that exposed the viewer to 131 doctors, scientists and cancer survivors from all over the world. I can truly say, it was a life changing experience for a number of cancer sufferers I know. Chemotherapy and 'Big Pharma' don't come out of the series in a good light. I recommend anyone about to start chemo view the relevant DVD, before beginning their treatment. See Appendix 3 for more details.

Finally, I very much enjoyed reading Bill Henderson's report "How to Cure Almost Any Cancer at Home for $5.15 a Day. Sadly, Bill passed away two years ago from a non-cancer related illness.

Chapter 22.

Future Developments

The world-wide prostate cancer research effort has never been greater than it has been in 2019. There are more than 800 clinical trials underway to take new drugs and therapies to their adoption into clinical practice. Most of these trials will fail, but the data accumulated in the successful trials and even those that have failed, will assist in bringing better treatments forward and hopefully, lead to a sustainable cure or vaccine.

In this chapter, a number of significant developments are considered. Some hold great promise, but again the majority are likely to fall by the wayside. The developments that follow are not listed in in any particular order.

Immune Cell Banking

Scientists in both the US and UK believe it is possible to strengthen the body's fight against cancer by transplanting immune cells from healthy donors to people with cancer. Professor Adrian Hayday of London’s Francis Crick Institute, is spear-heading this major research effort.

It is hoped these ‘immune-system transplants’ will improve the body’s natural ability to fight against the cancer, essentially giving the immune system the ability to eradicate cancer cells. Until recently, researchers believed that immune cell transplants would not work as the body would simply reject the new cells and the immunosuppressant drugs required would cause side effects that outweighed the benefits. However, researchers were surprised to discover that the transplanted immune cells actually survive well in the body, making the transplants a viable option.

“We’re seeing impressive results with cells called natural killer cells, explained Hayday. “It’s very early days, but there are patients receiving them in this next year (2019) and the year after (2020), and the nice feature is, unlike other immunotherapy, these cells aren’t rejected.”

Hayday's team uses immune cells called gamma delta T cells, instead of natural killer cells. In November 2018, they published a study in Nature Immunology showing that these T cells can be used to identify and kill dangerous cells within the body.

“If these transfusions work, as the early trials suggest they may, then establishing and maintaining donor cell banks is a realistic concept, albeit practically challenging," Hayday said. His team has started to develop one of these ‘immune banks’ that store immune cells ready to be transplanted into patients, similar to blood banks today.

ProscaVax Vaccine

OncBioMune Pharmaceuticals, Inc., a US clinical-stage biopharmaceutical company engaged in the development of a proprietary therapeutic prostate cancer vaccine immunotherapy, announced in March 19 that the Phase 2, randomized study of ProscaVax in patients with clinically localized prostate cancer versus active surveillance had started enrolment.

Although many patients with low-risk localized prostate cancer can be safely monitored with an Active Surveillance strategy in lieu of up-front treatment with surgery or radiation, about half of these patients will ultimately have to undergo treatment due to worsening of their disease. Thus, patients with localized prostate cancer need improved therapies to help prevent worsening of their disease and avoid the side effects of surgery or radiation. This study will evaluate the safety and efficacy of ProscaVax (Prostate-specific antigen (PSA) / Interleukin-2 (IL-2) / Granulocyte-macrophage colony-stimulating factor (GM-CSF)), in patients with localized prostate cancer compared to patients monitored on Active Surveillance.

"In general, this population of patients have two very different options. Either go into active surveillance waiting to see if there is progression of their cancer or have intensive local therapy, which can leave these patients with significant side effects. The goal which we are trying to obtain with this immunotherapy approach is to give these patients a third option which has more intervention than Active Surveillance, but with less toxicity than surgery, radiation therapy, or hormonal therapy," commented Dr. Brian Barnett, Chief Executive Officer at OncBioMune. "Phase 1 data underscores a strong safety profile for ProscaVax, while potentially moderating disease progression as measured by PSA doubling time. The start of this study represents a major milestone for our company."

The Phase 2 study will enrol 120 men with clinically localized prostate cancer who have received no prior therapy for prostate cancer. (The primary endpoint for the study will be an analysis of the number and percent of patients with progression at two years in each arm. Statistical assumptions are a 35% progression rate within two years in the control arm and decrease to 15% progression rate in the treatment arm). If this trial is successful and the vaccine comes to market, it will revolutionise low risk localised prostate cancer treatment.

Ribosome-Targeting Drugs

An Australian research team, including researchers from Monash University, the Peter MacCallum Cancer Centre and the University of Adelaide, have developed a method to grow (and study) human prostate tumours in the laboratory which has formerly been an extremely difficult task. This has yielded 10 new long-term growing tumours which have shown that the genetic nature of these tumour cells remain similar for hundreds of days. This allows the study of specific tumour types in detail, over multiple experiments.

To test a range of drugs for their ability to stop tumour growth, the researchers concentrated on four of the 10 tumours. These four tumour types were resistant to Enzalutamide or Abiraterone. All four tumour types responded to a combination of drugs that targeted a complex unit of molecules called a ribosome. (Ribosomes are an essential part of any cell; they make proteins using information from genes). This promising new treatment is a combination of two drugs that inhibits protein production by ribosomes.

"These lab-grown tumours have enabled us to rapidly compare different treatments and identify those that cause the most striking reduction in tumour growth," Dr Lawrence, one of the lead authors, said. "We developed a novel combination of two drugs that suppresses the growth of aggressive prostate cancer cells that do not respond to other treatments," he said.

Ribosome-targeting drugs are already in clinical trials for blood and breast cancers. Successful conclusion of these trials might accelerate clinical trials for aggressive prostate cancer. However, their introduction into a clinical setting is at least five years away.

Machine Learning combined with Flow Cytometry to identify High Risk Prostate Cancer

Anixa Biosciences, Inc., San Jose, CA., has developed a machine-learning system to predict the risk of either having an aggressive form of prostate cancer or lower grade PCa/BPH based upon the flow cytometry immune-phenotyping of myeloid-derived suppressor cells (MDSCs) and lymphocyte cell populations.

Highly complex science that offers great promise. Some years away from clinical uptake.

Computer Mutational Analysis Detects High Grade Prostate Cancer

A Danish and German team of cancer researchers have used cancer patient data to develop a computer model that can differentiate between aggressive and non-aggressive disease in early stage patients (under 55 years of age). The team chose younger men for their study to allow them to observe their tumour growth over a maximum time period.

Some 300 men had their entire cancer genome sequenced to characterise all mutations present in their tumours. With genome sequencing, it is possible to tailor the treatment of the individual - called personalised medicine. The patients included in the study were all ‘early onset’ patients

“If we have a patient with a particular set of mutations, we can use the model to predict the most likely next mutation that the patient will experience at some point - and how it will affect the patient's clinical situation. As an illustration, we can predict with some probability that if you have mutation A, you are likely to get mutation B before you get C. We can also predict if the next mutation is likely to change the clinical outcome of the disease,” said group leader and co-author of the study, Joachim Weischenfeldt, BRIC, UCPH, University of Copenhagen.

The model is currently being implemented at a prostate cancer clinic in Germany and is expected to be in wider clinical practice in both countries within 3 years. The researchers have also discovered the enzyme that appears to trigger some of the first mutations in prostate cancer.

Despite a massive international research effort, it is not known precisely what initiates prostate cancer. However, due to their focus on the earliest detected tumours, the researchers have uncovered a mutational mechanism involving an enzyme called APOBEC. This enzyme may help trigger the disease - i.e. trigger some of the very first mutations in prostate cancer.

“We hypothesise that this enzyme mutates the prostate cells at a low, but constant rate. Each time the cell divides, APOBEC is likely to cause mutations. If you have early-onset prostate cancer, you may have a couple of mutations caused by APOBEC. Twenty years later, you may have 10-20 mutations,” commented co-author Dr Jan Korbel, group leader at EMBL.

Joachim Weischenfeldt added; “The most common oncogene in prostate cancer involves a certain fusion gene. The APOBEC enzyme may contribute to the formation of this fusion gene. We cannot say that there is causality, but there is a strong correlation between mutations caused by APOBEC and other alterations such as this fusion gene.”

The researchers have also made a very important discovery when they found a prostate cancer oncogene (ESRP1) which is associated with very fast-dividing and highly aggressive prostate cancer. In the study, the researchers were able to show that the oncogene ESRP1 may be used as a possible new biomarker to detect whether a patient will have aggressive prostate cancer. They have now validated this on a cohort consisting of 12,000 other patients with the same type of cancer.

Scientists at the University of York and the University of British Columbia have found a way of distinguishing between fatal prostate cancer and manageable cancer, which could reduce unnecessary surgeries and radiotherapy. They team have designed a test that can pick out life-threatening prostate cancers, with up to 92% accuracy.

To find the different levels (Gleason score) of prostate cancer, scientists have to identify genes that have been altered in different cancer types. The team analysed more than 500 cancer tissue samples and compared them with non-cancer tissue to search for patterns of a chemical group that is added to part of the DNA molecule, thus altering gene expression.

Professor Norman Maitland from the University of York's Department of Biology said, "The challenge in prostate cancer is how to look at all of the patterns within a cell, and hone in on the gene activity that suggests cancer, and not only this, what type of cancer - dangerous or manageable? To put it another way: how do we distinguish the tiger cancer cells from the pussy-cat cancer cells, when there are millions of patterns of chemical alterations going on, many of which will be perfectly healthy?"

The team needed to eliminate the 'noise' of the genetic patterns that make individuals unique, to leave them with the patterns that indicate cancer. They were able to do this using a computer algorithm, which left the team with 17 possible genetic markers for prostate cancer.

Dr Davide Pellacani, who began these studies in York, before moving to the University of British Columbia, said, "Using this computer analysis, not only could we see which tissue samples had cancer and which didn't, but also which cancers were dangerous and which ones less so. Out of almost a million markers studied, we were able to use our new tools to single out differences in cancer potency."

The team are now investigating a further trial with new cancer samples, and hope to involve a commercial partner to allow this to be used for patients being treated in the UK National Health Scheme.

Natural Killer Cells activation by Chimeric Antigen Receptors

Masonic Cancer Centre members Aaron LeBeau, PhD, and Branden Moriarity, PhD, from the University of Minnesota Medical School used cutting-edge genome engineering technology, to develop methods to generate Chimeric Antigen Receptor (CAR) Natural Killer (NK) cells from NK cells in the blood.

LeBeau's and Moriarty's research focused on using the patient's own immune system to fight prostate cancer. Currently, cells known as T cells are used as a therapy to kill invading cancer cells and help give the patient's immune system a boost. But LeBeau and Moriarty have developed a way to use Natural Killer (NK) cells which are found in the body and can kill tumour cells. Using a chimeric antigen receptor for targeted activation, the CAR NK cells will hunt down and eliminate drug-resistant prostate cancer cells. NK cells don't require the same donor matching that T cells do, which could cut down the cost of CAR NK cell therapies compared to CAR T-cell therapies, making it a more accessible therapy.

"Our goal is to have a CAR NK cell therapy into the clinic for prostate cancer patients within a few years," said LeBeau. "We believe that it will prolong the life expectancy of, or even cure, men with aggressive prostate cancer."

Cell Senescence – Putting Cancer Cells to Sleep

Dr Tim Thomas and Dr Anne Voss of the Walter and Eliza Hall Institute, Melbourne, Australia have spent years investigating KAT6 proteins for cancer treatments. KAT6A and KAT6B are proteins that control embryonic development, and also induce cancer. Indeed, the gene for KAT6A is the 12th most frequently amplified gene in cancer cells. Shutting down KAT6 stops cancer cells dividing, which Voss and Thomas call ‘putting them to sleep’.

“The technical term is cell senescence. The cells are not dead, but they can no longer divide and proliferate. Without this ability, the cancer cells are effectively stopped in their tracks,” said Voss.

In their study published in Nature, Thomas and Voss describe the use of their adapted molecule WM-1119 to eliminate mice lymphomas, although quite high doses were needed. Thomas explained to IFLScience that KAT6A blocking is expected to work against a sub-set of cancers in a wide range of organs, with genomics making it increasingly easy to identify the patients who are likely to respond well. However, further modifications will be needed before testing in humans can begin, the risk of long-lasting side effects is low as KAT6A appears unnecessary in adults.

Starpharma’s Dendrimer Technology

Starpharma’s underlying technology is built around dendrimers - a type of synthetic nanoscale polymer that is highly regular in size and structure and well-suited to pharmaceutical and medical uses. Starpharma has two core development programs, with one applicable to solid tumours.

DEP® - Dendrimer Enhanced Product®: Starpharma’s DEP® drug delivery platform has demonstrated reproducible pre-clinical benefits across multiple internal and partnered DEP® programs, including improved efficacy, safety and survival. By joining the drug to a dendrimer construct, very large increases in drug solubility have been achieved, which can enhance the ‘bioavailability’ of the drug. It can also avoid the need for the use of problematic and potentially dangerous additives in drug formulations, helping to improve the safety profile of the active agent.

Starpharma has two internal DEP® products – DEP® docetaxel and DEP® cabazitaxel - in clinical trials with patients with solid tumours. Both drugs are front-line prostate cancer chemotherapies. Early results are very encouraging with minimal patient side effects when compared to those experienced by either drug alone. More importantly, the efficacy of these DEP® drugs has been remarkable.

Starpharma’s partnered DEP® programs include a multi-product DEP® licence with AstraZeneca, which involves the development and commercialisation of two novel oncology compounds, with potential to add more. In June 2019, Starpharma signed a Development and Option agreement with AstraZeneca to progress a DEP® version of one of AstraZeneca’s major marketed oncology medicines.

This technology is likely to significantly change prostate cancer chemotherapy if and when it reaches widespread clinical usage within about three years.

Chimeric Antigen Receptor T-Cell Therapy (CAR-T)

Chimeric antigen receptor T-cell therapy is a promising new immunotherapy that is the subject of a great research effort around the world. It is already approved by the FDA for certain blood cancers.

T-cells are removed from the patient’s blood in the lab and are genetically engineered, before being re-infused into the patient. Solid tumours, as found in prostate cancer, are a challenging target for many reasons, including CAR-T cells are not transported efficiently into the interior of solid tumour masses, and the suppression of T cell activity in the hostile tumour micro-environment.

Future directions in the development of CAR-T for prostate cancer treatment will focus on high specificity and efficacy, low toxicity and immune-suppression, and synergy with other tumour therapies. It is expected that CAR-T technology will be successfully applied in clinical prostate cancer therapy in the near future, but only with men with appropriate physiology (DNA genes, etc.).

(The technology presented two pages back is a significant variant to ‘standard’ CAR-T cell therapy).

Protein Degrader ARV-110 enters Phase 1 clinical trial

Arvinas Inc., a US-listed biopharmaceutical company, has created a new class of therapies that degrades disease-causing proteins. In June 19, it announced that its PROTAC® Protein degrader, ARV-110, had been granted Fast Track designation by the FDA for the treatment of men with mCRPC whose disease had progressed after treatment with two or more systemic therapies. ARV-110 is an orally bioavailable PROTAC protein degrader designed to selectively target and degrade the androgen receptor protein.

John Houston, Ph.D., President and CEO of Arvinas said, “Due to its ability to iteratively degrade the AR protein, we believe, ARV-110 could represent a meaningful new therapy to improve the lives of patients battling mCRPC, and for whom current therapies are not effective. The Fast Track designation by the FDA recognizes the urgency for improved treatments for these patients.”

First Patient dosed in a Phase 2 study with LiPlaCis (Cisplatin)

LiPlaCis® is an intelligent, target-controlled liposome formulation of one of the world’s most widely used chemotherapies, cisplatin. LiPlaCis® has shown very promising results in an ongoing Phase 2 study in patients with metastatic breast cancer.

The prostate cancer study will examine if patients respond to LiPlaCis® in the same way as patients with breast cancer, and the first patient was recently dosed at the University Hospital in Herlev, Denmark. The fifteen-man trial was selected using the diagnostic predictive tool -- DRP® (patients’ tumour genes are first screened, and only the patients most likely to respond to the treatment are treated).

“It is known that platin products are active in prostate cancer, but previous clinical studies have not been able to show sufficient effect to obtain marketing approval. We believe this is mainly due to treating a too-broad patient population and the trial will examine if the DRP can identify the individuals, who benefit from the LiPlaCis treatment, as we can do in breast cancer,” said Peter Buhl Jensen, M.D., CEO of Oncology Venture A/S.

ProstAtak® Immunotherapy in Patients undergoing Active Surveillance

The ‘Ulysses’ randomized controlled Phase 2 trial of the immunotherapeutical ProstAtak® with the drug valacyclovir for newly-diagnosed men on active surveillance, began recruitment in 2016. ProstAtak® is a gene-mediated cytotoxic immunotherapy (GMCI™ - aglatimagene besadenovec (AdV-tk) plus oral valacyclovir) for treatment of localised prostate cancer. GMCI is an ‘off the shelf’, low-toxicity immunotherapy that stimulates a patient's own immune system to generate a robust and precise response against their cancer. If the therapy proves efficacious at the conclusion of the study in late 2020, ProstAtak® promises to be the first and only therapeutic pharmaceutical available for newly-diagnosed prostate cancer.

Candel Therapeutics is also conducting PrTK03, a registration trial with ProstAtak® for the treatment of intermediate-high risk localised prostate cancer patients undergoing radiation under a Special Protocol Assessment approved by the FDA.

Topsalysin Phase 3 trial approved for Intermediate Risk Localised Prostate Cancer

Sophiris Bio Inc., a late-stage clinical biopharmaceutical company, in July 19, received European Medicines Agency approval for their Phase 3 clinical trial protocol for the use of their injectable topsalysin for men with intermediate-risk prostate cancer. Topsalysin is a highly potent ablative agent that is selective and targeted in that it is only activated by enzymatically-active PSA, which is found in high concentrations in the transition zone of the prostate, and in and around prostate tumour cells. The increasing use of mpMRI and advances in software in merging previously obtained mpMRI images with real-time 3D ultrasound images enables urologists to more accurately locate tumours within the prostate when taking biopsies. This increases the accuracy with which men with clinically significant lesions are identified. It also enables the injection of an ablative agent, such as topsalysin, directly into previously identified clinically-significant tumours located within the prostate.

Approximately 700 men will be equally randomized to receive a single administration of either topsalysin or placebo with initial results, expected at 12 months. Hopefully, a positive outcome will lead to early clinical approval. Topsalysin has already undergone a successful Phase 3 trial for BPH.

Progenics AZEDRA: Hope for men with Neuroendocrine Tumours?

In June 19, Progenics Pharmaceuticals Inc. announced that they had reached agreement with the FDA on the clinical development plan to help bring forward their drug AZEDRA (iobenguane I 131) for the treatment of patients with unresectable or metastatic neuroendocrine tumours (NET's) who are MIBG avid. (NET's over-express the norepinephrine re-uptake transporter on their cell surface. MIBG is a known sub-strate for the transporter and, therefore, MIBG avidity can be used to determine which patients are most likely to respond to AZEDRA therapy).

Mitochondrial-based Therapeutic Strategies for Eradicating Cancer Stem Cells

A number of research groups are making progress in their drug repurposing efforts, to develop a series of new therapeutics, by focusing on key mitochondrial targets. These therapeutics are designed to kill CSCs as well as various types of progenitor cells. CSCs and progenitor cells (< 5% of all cancer cells) are thought to be the most dangerous, as they behave as tumour-initiating cells in the body and can undergo metastasis; in contrast, 'bulk' cancer cells are largely non-tumourigenic. The therapeutics being used in this research effort are all existing approved drugs, which would see any new compound go straight to a Phase 2 trial.

The mitochondria in all human cells consists of more than 1000 proteins that are encoded by the nuclear genome. Researchers are assessing the potential prognostic value of these proteins as novel biomarkers and companion diagnostics. They hypothesis that the over-expression of a given mitochondrial protein in cancer cells and CSCs may be associated with tumour recurrence and metastasis, due to the emergence of drug resistance, ultimately resulting in treatment failure. It is early days, but progress is being made.

Zinc Therapy

Many years ago, researchers discovered that all men with prostate cancer showed much lower zinc levels than in men without malignancy. At that time, it was suggested that an increase in foods with high zinc content or zinc supplements, would enable the absorbed zinc to ‘fight back’ against the cancer. Sadly, this led to negligible impact, as the physiology of the prostate, which is still not fully understood, did not support such zinc absorption. Recent research, which has contradicted earlier research, has determined that the decrease in zinc is achieved by the down-regulation of ZIP1 zinc transporter, which prevents the uptake and accumulation of cytotoxic zinc levels. Costello et al., (University of Maryland School of Dentistry)[1] suggested that prostate cancer is a ‘ZIP1-deficient’ malignancy. He further noted that testosterone and prolactin are the major hormones that similarly regulate the growth, proliferation, metabolism, and functional activities of the acinar epithelial cells in the peripheral zone of the prostate. (More than 80% of prostate cancer starts in peripheral zone). Most men with advanced prostate cancer include ADT in their treatment regime. This substantially eliminates testosterone from the body. Many men progress under the influence of prolactin to CRPC after extended ADT. The relationship between testosterone and prolactin presents an opportunity for the prevention and treatment of advanced prostate cancer. In the paper referenced above, (and in a follow-up June 19 paper that focused on cabergoline), Costello[2] proposed a clioquinol/cabergoline treatment regime that they suggest, will be ‘efficacious for aborting terminal advanced prostate cancer.’ FDA policies presently permit this treatment regime for such terminally-ill patients.

The acinar cells of the peripheral zone are zinc-accumulating as well as citrate-producing. In prostate cancer, the decreased zinc inhibition of citrate production is removed, and the malignant cells show major decreased citrate levels. These factors allow the use of in situ (in body) magnetic resonance spectroscopy imaging (MRSI) for the identification of normal and malignant cell activity in the peripheral zone. An excellent diagnostic tool.

Clioquinol lotion (zinc ionophore; 5-chloro-7-iodoquinolin-8-ol), when externally applied, facilitates zinc transport and accumulation in the ZIP1-deficient prostate cancer cells and induces cytotoxic effects. Cabergoline (a dopamine agonist, Dostinex) is used to significantly decrease prolactin production and release its cancer cell killing capability.

This possible therapy needs a considerably larger number of men to go through a controlled trial. It is appropriate for men contemplating its use, to present copies of the referenced scientific papers to their medical team for their review, so that they can advise the patient appropriately.

Mitochondrial Inhibitors

I was privileged to recently read Jane McLelland's best-selling book "How to Starve Cancer." The book is like a thriller, but at the same time, it is very inspirational and informative for all cancer sufferers and their families. The book starts with Jane being diagnosed with Stage 4 cervical cancer at the age of 30 and being given 12 weeks to live. As a physiotherapist, she was not prepared to accept her diagnosis and immediately started researching natural therapies and older FDA-approved drugs. Of particular initial interest to me was her taking doxycycline (a general-purpose antibiotic discovered 62 years ago) and intravenous Vitamin C. Over time she beat the cervical cancer, but about five years later, found she had a sizeable tumour in a lung. This saw her undergo radiation therapy of the tumour, but when this failed, she had a third of her lung removed. Sadly, the radiation led to her contracting leukemia, which she then beat using her integrative therapy approach (Both conventional and unconventional therapy). Today she is in good health and has spent the interim period refining her research into cancer including the development of a MetroMap of treatments for abnormal cell signaling and pathway issues. Go to my web site at www.anabcofprostatecancer.com.au to access the MetroMap V2.0 modified for prostate cancer.

What has this got to do with mitochondrial inhibitors? It's about killing 'almost immortal' cancer stem cells. CSC's are involved in tumour recurrence, distant metastasis and therapy-resistance, driving poor clinical outcome in advanced cancer patients.New therapeutic strategies are necessary to identify and eradicate CSCs which presently remains an unmet medical need.

De Francesco, EM, et al., in their paper "Vitamin C and Doxycycline: A synthetic lethal combination therapy targeting metabolic flexibility in cancer stem cells" (Oncotarget. Sep 2017) outlined how they used doxycycline (hit-1:targeting the mitochondria) to 'weaken' the CSC's before 'attacking' them further with high doses of intravenously-delivered Vitamin C (hit-2: targeting glycolysis) and a selection of other compounds (berberine, and one or more of the FDA-approved drugs: Atovaquone, Irinotecan, Sorafenib, Niclosamide, Chloroquine, and Stiripentol).

The research group concluded: "We have identified a novel metabolic mechanism by which CSCs successfully escape from the anti-mitochondrial effects of doxycycline, by assuming a purely glycolytic phenotype. Therefore, doxycycline-resistant CSCs are then more susceptible to other metabolic perturbations, because of their metabolic inflexibility, allowing for their eradication with natural products and other FDA-approved drugs. Thus, understanding the metabolic basis of doxycycline-resistance has ultimately helped us to develop a new synthetic lethal strategy, for more effectively targeting CSCs."

Work continues to bring this 'therapy' into a clinical setting. (As they are natural compounds and out-of-patent drugs, Big Pharma won’t be interested).

Bi-specific Antibody Therapy

Bi-specific T-cell engagers (BiTEs) are a new class of immunotherapeutic molecules which enhance a patient’s immune response by helping T cells target specific tumour cells. A Phase 1 prostate cancer trial (NCT03792841) using Pasotuxizumab BiTE® (Amgen) is progressing in mCRPC men resistant to abiraterone and/or enzalutamide and also to at least one taxane-based chemotherapy.

Three of 16 patients had a >50% PSA decline, but 14 of 16 had some level of PSA decline. Two patients had long-term PSA responses (one for 14 months and the other for 19.4 months). The latter patient had a complete response in soft tissue and evidence of response in bone metastases as shown by PSMA PET/CT. Only one patient had a serious adverse event (fatigue). The trial results to date suggest that a new class of agents for mCRPC men might be in sight.

Other bi-specific antibody agents are entering clinical trials. One bi-specific antibody agent, called a DuoBody®(Genmab), also targets CD3 and PSMA. (Dual targeting: the DuoBody agent can be used to bind multiple targets, to block multiple pathogenic pathways, target tumour heterogeneity, increase specificity, and/or synergistically induce enhanced therapeutic effects. They can also be used to bind multiple sites on one target). A further bi-specific antibody will soon enter a clinical trial with the goal of marrying CD3 positive T cells to STEAP1-expressing prostate cancer cells.

EZH2 inhibitors

The so-called enhancer of zeste homolog 2 (EZH2) is an enzyme encoded by the EZH2 gene. The mutation or over-expression of EZH2 has been linked to many forms of cancer including prostate cancer. The ProSTAR study presented data, at the American Association of Cancer Research 2019 meeting, on CPI-1205, a small molecule inhibitor of EZH2. mCRPC patients, who previously progressed after either abiraterone acetate or enzalutamide, were treated in multiple dosing groupings, resulting in some patients with PSA, RECIST 1.1 and/or CTC reductions. Two clinical trials (not yet listed on clinicaltrials.gov) are planned to evaluate CPI-1205 in a Phase 2, single-arm combination with abiraterone acetate and prednisone and in another randomized trial in combination with enzalutamide. Below, are other ongoing trials that are actively accruing patients, including those with mCRPC, to receive agents that either directly inhibits EZH2 or that affect other proteins that physically interact with EZH2:

Phase 1b/2 ProSTAR CPI-1205 (NCT03480646)

Phase 1 PF-06821497 (NCT03460977)

Phase 1 Tazemetostat (EPZ 6438) (NCT03010982)

Phase 1 MAK683 (NCT02900651)

Studies to evaluate the treatment of mCRPC patients with a combination of an EZH2 inhibitor and an immune checkpoint inhibitor are being planned.

Calibr CCW702 Immunotherapy for mCRPC

Calibr, the drug development division of Scripps Research, announced in August 19 that the FDA has cleared its investigational new drug application for CCW702, a novel immunotherapeutic for the treatment of patients with mCRPC. “CCW702 has the potential to be effective in patients who have failed prior treatments and have exhausted their treatment options, because it works differently than traditional chemotherapeutics and androgen deprivation therapies,” said Travis Young, PhD, VP of Biologics at Calibr, who led the pre-clinical development of the molecule.

CCW702 is a first-of-its-kind molecule designed to redirect a patient’s own immune system to eliminate malignant cancer cells. The molecule uses a unique design that combines the specificity of a validated imaging agent for prostate cancer with the potency of immunotherapy. In pre-clinical work, this design proved highly effective at completely eliminating tumours in animal models of prostate cancer.

Veyonda® Enhances Radiotherapy in Prostate Cancer Treatment

Noxopharm, an Australian clinical-stage drug development company, in early December 19 announced the positive end-of-study data from their DARRT Phase 1b study (NCT03307629). Their proprietary treatment Veyonda® combined with low dose palliative radiotherapy (to a single lesion only) resulted in reductions in tumour size; reductions in pain for 62% of the men; and reductions in PSA levels for 31% of these men with the PSA drop varying between 61 and 98%. Even though the trial was very small with only 25 men and of only 6 months duration, the results obtained were very impressive as they were achieved in men with end-stage mCRPC with no further treatment options available to them.

Veyonda® is a suppository dosage formulation of the experimental anti-cancer drug, idronoxil. Idronoxil specifically inhibits the oncogene, Ecto-NOX disulphide-thiol exchanger type 2, leading indirectly to inhibition of the key secondary pro-survival messenger, sphingosine-1-phosphate. This enhances the DNA-damaging effects of radiotherapy, as well as promoting trafficking of the body's innate and adaptive immune systems.

Nine of fifteen men responded to a combination of Veyonda and EBRT with stable disease (plus 1/15 had only a partial response) at 6 months. The trial met its primary end point of safety with no significant or dose-limiting toxicities. The scope of this study is expected to be expanded internationally in 2020 and an IND application to the FDA and other regulatory bodies will follow.

Niclosamide and Indomethacin

Lastly, rather than focus on one technological breakthrough, it is appropriate to illustrate the extent of prostate cancer research ongoing in hundreds of research groups around the world, by illustrating the research program of a single research institution, in this instance the Urologic Surgery team at the UC Davis Comprehensive Cancer Centre. Print space only allows a cursory look at their prostate cancer research activities. They are working on a number of anti-androgen therapies and have identified several novel resistance mechanisms that include AR-V7 and AKR1C3.

They have discovered that niclosamide, an FDA-approved medicine commonly prescribed to fight worms, is a potent inhibitor of AR-V7 and it can dramatically enhance the efficacy of anti-androgen drugs such as enzalutamide and abiraterone (Clin Cancer Res 2014, Oncotargets 2016). Based on encouraging preclinical data, they have reformulated niclosamide and received FDA IND approval for Phase 2/3 clinical trials in CRPC patients.

They also determined that indomethacin, a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation, can inhibit AKR1C3 activity and significantly inhibits enzalutamide-resistant tumour cell growth. (AKR1C3 - a gene that is over-expressed in prostate cancer). While indomethacin alone significantly suppressed tumour growth, the effect was further enhanced in combination with enzalutamide (Cancer Res 2015). Clinical trials to test targeting AKR1C3 pathways with indomethacin to improve enzalutamide therapy are currently progressing.

Summary

I could have selected further examples of developing therapies that might offer the promise of good outcomes for advanced prostate cancer patients. The massive research effort going into cancer generally and hormonal breast and prostate cancer research, in particular, will see a constant flow of new therapies that advance into clinical trials. Sadly, the time from the start of a Phase 1 clinical trial to the availability of the therapy in a clinical setting is far too long – typically 3 to 6 years.

Most of the developments included in this chapter are already the subject of clinical trials. Some are still recruiting patients; others are fully subscribed. Others will announce trials in due course. Many of these potential therapies offer patients joining one of these clinical trials, a possible opportunity to get on top of their mCRPC. Their participation also offers them an opportunity to contribute to the science and as such, help fellow or future sufferers.

Chapter 23.

The Role of Support Groups

The first line of support that you will need after being diagnosed with prostate cancer, and throughout the treatment phase, is your immediate family. It is essential to have them understand what you are going through; for them to understand your treatment regimen; and for them to be there to help you digest what you are told by your medical team. Of paramount importance is your spouse, or partner. The consequences of prostate cancer treatment, whether you are diagnosed at the local; advanced local or metastatic cancer levels, are of huge concern to your wife or partner. After all, there is a reasonable likelihood that your sex life might be compromised in the short or medium term or permanently. Perhaps of even greater importance is the psychological blow that being diagnosed with a life-threatening condition, might present you. Some men are able to cope with one, or both challenges very well, whilst others can just about go to pieces, and will need serious professional help to assist in regaining a positive mindset that allows them to fight the disease.

It is a battle and often it is not easy, particularly if you are diagnosed with prostate cancer at the higher risk of the scale. Your children should also be brought into the loop at an early stage. They need to understand the challenges you face and allow them the chance to participate in your recovery process. Of course, if they are under-age children, it would be far more confronting to them to know that their father has a life-threatening illness, so discretion as to what they are told is appropriate. Most couples have a circle of close friends. They too should be selectively briefed and also add themselves to the growing army of people helping you to get back to full health again, as quickly as possible. You also probably have colleagues or superiors at work who need to know that you are committed to a treatment regimen in order to restore your health. Your recovery will ensure that you continue to make an appropriate ongoing commitment to your employer’s activities.

You will find that your medical team can only spend limited time with you at each stage of the diagnosis, testing and treatment phases of your condition. You cannot possibly ask all the right questions and get sufficient information from your doctors, to enable you to make the most appropriate and correct medical decision to suit your condition and your circumstances. Sure, it’s okay to spend hours on the internet researching options. The problem is that there is so much information out there, that it is very hard to get the right information that matches your unique position. (Author’s Note: I’ve spent hundreds and hundreds of hours researching for this book, with the majority of information being accessed via the Web (PubMed, etc.). I have also spoken to dozens of prostate cancer survivors and many medical professionals, in addition to the countless books read on the subject).

Even medical doctors, who have been diagnosed with prostate cancer, don’t know which questions to ask their urologist or oncologist. I played golf with a general surgeon a few years ago, who had had a radical prostatectomy six months earlier. Apparently, he had a good outcome from the surgery. However, he had almost no knowledge of the other alternative treatments available to him. He appeared vague about the two forms of brachytherapy available and had no knowledge of proton beam therapy, HIFU and other focal treatments. He did not tell me his Gleason Score, so I am unable to speculate as to whether or not he needed the treatment that he had. (Remember I am NOT a medical doctor). He had not considered radiation therapy either. I hypothesise that he had gone to see a urologist, who generally favoured a surgical solution to treat prostate cancer, and took the urologist’s advice to have his prostate removed. Now, there is nothing wrong with his actions, other than the suggestion that he did not consider other options that might have given him an even better outcome than that achieved. Engagement with others who collectively have had a variety of treatments at a prostate cancer support group might have alerted him to other, perhaps more beneficial alternatives.

One of the issues when you question men who have had prostate cancer surgery, radiation treatment, or any other method of treating the cancer, is often too hard to pursue: Are you impotent? Are you incontinent? These are extremely private questions that really cannot be asked other than by a doctor. A few men volunteer answers to these questions before being asked, as they know they are the two most vital questions, after the most important one of all, and that is, will you be free of the cancer after treatment and survive?

Many men attending prostate support groups have been through the mill and attend these groups with a view to helping others. Others, who still have to decide on a course of treatment, attend as a learning experience. These groups often have a different modus operandi. Some meet informally over lunch; others under the auspices of a hospital or regional health centre; others are run by not-for-profit organisations like Cancer Councils; etc. It is best to access the Internet to find which groups are active in your area and how you might find out more information about attending, etc.

A few years back, I bought a copy of Dr Jay Cohen's book "Breakthroughs in Prostate Cancer 2014." (Replaced in 2018 by "Prostate Cancer Breakthroughs: The New Options You Need to Know About."

The original title is an excellent book written by a medical doctor who practices medicine outside the genitourinary field. He was diagnosed with prostate cancer in 2011 and was booked in for surgery after a process that appeared to be very similar to that of the general surgeon that I referred to earlier. He was sent to see a nurse specialist who provided him with information about the standard treatment options. She answered his many questions, as well as suggesting he might want to investigate a local independent support group called the "Informed Prostate Cancer Support Group" (IPCSG). This group meets monthly on a Saturday, a day that prevented Dr Cohen attending, due to his work commitments. However, a few of their members meet informally for lunch each week. The attendees use the lunch to update their colleagues on their status, treatment outcomes, etc. They also discuss new information that they might have gleaned from news reports, medical literature or from the Web.

Dr Cohen ‘discovered’ DCE-MRI and Colour Doppler Ultrasound at one of these lunches. His doctor had not mentioned either of these important tools in the diagnosis of prostate cancer, to him. He also became aware that the IPCSG offers more than 30 DVDs prepared from their monthly meeting lecturers’ presentations. He became a regular attendee at these luncheons. In short, his attendance at the lunches convinced him to have a Colour Doppler Ultrasound and a DCE-MRI as a follow-up. The results from these two tests convinced him to join the ‘Active Surveillance’ brigade. The IPCSG has a very interesting web site with a host of information and links to other pertinent prostate cancer diagnoses and treatment. It also lists details of the DVD’s that are for sale at $10.00 each. Access their web site via Appendix 3.

An international prostate cancer support group, called Us TOO International, Inc., exists that has about 225 chapters worldwide. A significant number of these exist in the USA. Support groups are listed in 6 countries as follows:

USA (about 200); The Netherlands; Spain, Australia, Bahamas; and Canada.

Access the web site via Appendix 3. Us Too International have been operating for 24 years and have the following mission statement:

“The mission of Us TOO is to help men and their families make informed decisions about prostate cancer detection and treatment through support, education and advocacy.”

I did NOT attend a structured support group, but rather called on the experiences of four or five close friends and my brother, all of whom had faced prostate cancer before my diagnosis. Two reasons contributed to me not joining a formal group. Perhaps the most important reason was my personality. As a bit of a loner, I like researching and discovering things myself. After a 45-year career in the commercial side of science and medicine, I am well-versed in investigative research and understanding technical and medical jargon. A lesser reason for not attending a support group, was geographical, as I used to live 60 miles (100kms) from Sydney, Australia. Trips to the city required a 90 minutes road trip or a 30-minute drive to the nearest rail link followed by an 80-minute train trip.

However, in September 2014, I discovered that the Prostate Cancer Foundation of Australia has grown their number of support groups to 165, with one group meeting about 25 kilometres from my then home. I attended this support group's monthly meetings regularly until I re-located our home back to Sydney in July 2015. Doctors and other health professionals address the meetings which are usually attended by about 30 men, some with spouses, and a small number of area health continence nurses and a social worker.

A number of the Proton Beam centres support an independent alumni of past prostate cancer patients. The most well-known of these is "The Brotherhood of the Balloon" (called BOB for short) run by Robert Marckini and his daughter. (Some 7000 prostate cancer patients previously treated at the Proton Beam Therapy Centre at the Loma Linda University Medical Centre receive this newsletter, reunions and other benefits).[1] Robert has also authored an excellent book on prostate cancer titled "YOU CAN BEAT Prostate Cancer and You Don't Need Surgery to Do It." It is a very informative and an inspiring read.

So, don't forget to consider joining a prostate cancer support group.

PART 3: MY PROSTATE CANCER JOURNEY

Chapter 24.

My Prostate Cancer: Ongoing Research

In Part 1 of this book, I gave details of being diagnosed with prostate cancer and details of my follow up visit to Dr P., my first urologist. He had indicated that I was an excellent candidate for a radical prostatectomy. Using the Da Vinci® keyhole surgery system, I would have a short hospital stay and be back on the golf course in no time. However, whilst all surgical care would be taken to spare the nerve bundles that control erections, there could be no guarantee that I would maintain my ability to have an erection. Also, there was a possibility that I would also suffer from incontinence, particularly stress incontinence (the release of urine upon coughing). In fact, the chance of me having erectile dysfunction was rated at 24 to 29% with the figure for incontinence being around 30% at 6 months after surgery. Dr P advised that if I did suffer from erectile dysfunction after the operation, it was possible that my ability to have an erection might partially or wholly return over time. It might be assisted by taking Viagra, Levitra or Cialis before intercourse.

By the way, I should regress somewhat. During the consultation when I was told that I had prostate cancer, my urologist made a small drawing of my prostate and indicated where the cancerous tissue appeared in the prostate. It was present in both lobes with the left lobe containing a sizeable tumour. Nine of the 24 biopsy samples contained cancer cells. The reason I had so many samples was that I have permanent arrhythmia of the heart and take warfarin to thin the blood to lessen the risk of a stroke. I had to go on Clexane® injection treatment for the five days I was off warfarin. The larger than normal number of cores taken, would obviate the need for a medium-term follow up biopsy. I was pretty disappointed that there was no computer-generated image to show the size and distribution of the tumours. However, just being told I had cancer, didn’t get me going on this point. Also, there was no discussion about the option of active surveillance, probably because I had an intermediate risk cancer with a Gleason Score of 7 (3 + 4 which is far better than 4+3 as explained earlier in this book).

All of this was enough to put me right off the prospect of surgery. I have a couple of friends who I meet with once or twice a month in Sydney to discuss stocks and shares. John had had proton beam therapy in the USA some ten years previously. Paul had had a radical prostatectomy performed by one of Australia's leading urological surgeons about four years ago when he was 60 years of age. Whilst John and I had met Paul before his surgery, Paul was really a casual acquaintance, with us bumping into each other at investment presentations, conferences, etc. from time to time. He was unaware of proton beam therapy leading up to his surgery, nor was he made aware of it as a possible treatment by his urologist. He didn't get much input from his specialist about other forms of treatment either. He was given two choices: a radical prostatectomy or a course of external beam radiation therapy.

The various other radiation techniques such as low dose or high dose brachytherapy or HIFU, were not mentioned to him as options. When first diagnosed, Paul had a PSA of 12.5; with a Gleason Score of 7 (3+4) and his cancer was considered a Type 1c. He was unclear as to the number of biopsy cores taken and the number that contained cancerous tissue. Two thoughts come to mind, regarding Paul's decision to have surgery and his lack of understanding of his diagnosis and the various options that were open to him: firstly he had cancer and wanted to do whatever it took to rid himself as soon as possible of the scourge that is cancer and secondly, his medical team did not appear to share with him vital information that they should have, so as to give him real choice as to the alternative therapies open to him. In my view, this was not a good situation to have to face at a time of acute anxiety. Well, what was the outcome of the surgery? He had a complete inability to have an erection and incontinence to the point where he has to wear a urinary pad all the time.

My friend 'Michael', who I caught up with at my school reunion in South Africa, also had erectile dysfunction after surgery and even with pharmaceutical assistance, found sex a chore only to be endured for the benefit of his wife.

Side Effects of Current Treatments

% of Patients Treated

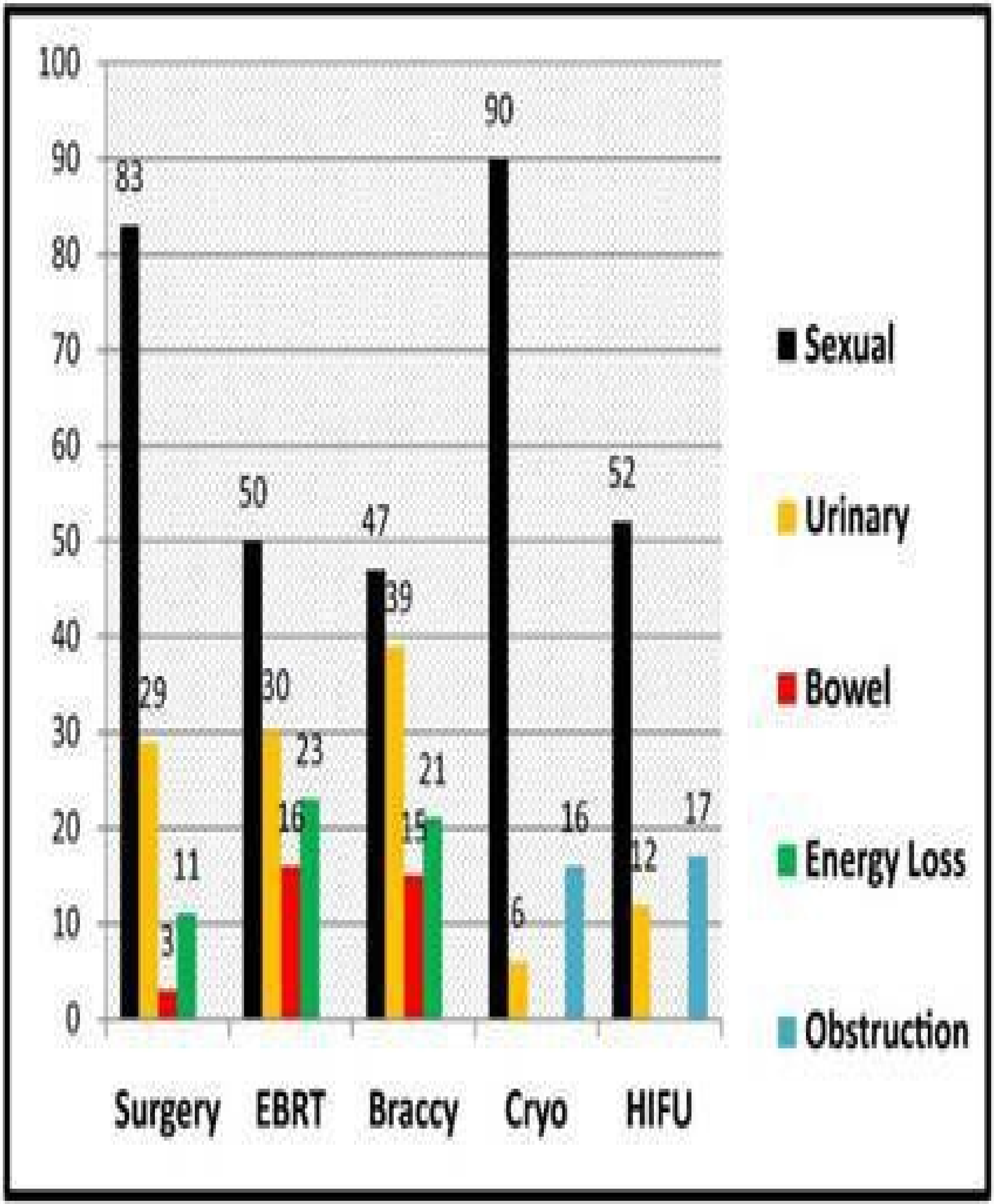


Chart reconstructed using data provided by **LaZure Scientific**

Graph: Courtesy of LaZure Scientific Inc. developers of LDAC technology

(About the above graph: The data was collected about 6 to 8 years ago. The widespread use of the da Vinci robot for radical prostatectomy and improved nerve-sparing techniques has seen the percentage of men with erectile dysfunction somewhat lower than shown above, probably in the 15 to 40% range).

Whilst researching my treatment options, I came across a book titled “Surviving Cancer with Proton Therapy: Road to Nami Island”, written by York L. Phillips and Curtis Poling. The central character in the book, called ‘Joe,’ undergoes successful proton beam therapy in Korea. However, in the lead up to deciding on this treatment, he visited a number of leading physicians each of whom recommended his speciality as being the most appropriate for Joe, considering his PSA, Gleason Score, etc. Now, all could be correct in their claim, but some treatment types might have been better than others. My wife tells me that I am often cynical. She is probably right as I saw the above example manifested by some of the medical specialists I encountered, whilst researching my treatment options and indeed in the preparation of this book.

Back to Paul. He became aware of proton beam therapy (PBT) when John and I were discussing it in his presence (This was during the period I was researching my treatment options). Paul was interested to learn more about John’s treatment at Loma Linda. Of course, he found out too late of the benefits available to men having treatments other than a radical prostatectomy. His interest and geno-urinary condition had quite an impact on me. It convinced me to do something as a layman (and a prostate cancer sufferer), to spread the word on the options that are available to newly-diagnosed men and to keep track of developments in the field.

At my second post-diagnosis meeting with my urologist, he asked me had I made a treatment decision. I told him that I definitely would not consider a radical prostatectomy, due to the unacceptably high incidence of erectile dysfunction and incontinence. I also told him that I wasn’t too keen on EBRT either. The main reason I advanced were:

The high prospect of loss of erectile function; the high incontinence risk; an inability to have further radiation should cancer return down the track; the slight possibility of secondary cancers forming as a result of the radiation dose received.

My research at this stage had focussed on two treatment formats: PBT and HIFU. My urologist was somewhat familiar with PBT, which he stated was still an experimental technique. (Some 100,000 men over 30 years had undergone PBT by this time!) He also said that it would be very expensive, would not be covered under Australian Medicare insurance scheme or by my private health fund, as it was only available in America. (Wrong - 15 PBT centres around the world accepted English-speaking men. This number has now tripled)!

Chapter 25.

Was HIFU the Answer?

My second technique of interest was High Frequency Ultrasound (HIFU) in which an ultrasonic probe is inserted in the rectum and the whole prostate gland is ablated (under precise computer control) by the ultrasonic energy. The system heats the prostate tissue to more than 70° C (158° F), thus killing the prostate and cancer tissue.

My interest in this procedure was because the treatment was quick and simple (a one-off 3-hour procedure), with a likelihood of fewer and less severe side effects. A search of the internet had indicated that about 6 urologists in Sydney used the technique. I also found a news release from one of the two HIFU instrument manufacturers congratulating one of Australia's most well-known and proficient cancer urologists for undergoing overseas training on their system a year earlier. He had begun to treat patients locally with their HIFU system. I happened to be acquainted with one of the doctors who used HIFU (from a previous golf match). Dr L practised at a prestigious cancer institute and was highly regarded in his area of speciality. A referral was obtained and a few weeks later I found myself running down the road from the station to get to my appointment on time after a late arriving train had intervened. Fortunately, the doctor was running 15 minutes late so I had time to cool down and feel like a proper person again before I saw the doctor.

Dr L examined my medical record and pathology report and did the regular digital rectal examination. No lumpiness was found during the DRE. We discussed HIFU. He advised that he still uses the technique but only sparingly, particularly in men in the late seventies and eighties. He was of the view that whole prostate gland ablation was too radical a solution in my case considering the size and distribution of the tumours in my prostate. (My tumours were all adenocarcinomas which are the most common prostate cancer tumour type). He suggested that high dose brachytherapy might be a more beneficial approach to take considering my age, physical fitness, pathology, etc. I suggested to him that my sample of one person (my brother) undergoing this type of treatment had shown a recurrence of the cancer eight years later. His response was that there is always a small percentage of patients who have recurrences, even after radical prostatectomies, or other forms of treatment. All it needs is for a few cancer cells to survive the treatment, and then to re-establish themselves as a threatening tumour over time. He suggested that he could refer me to a good radiation oncologist based at the hospital adjacent to his institute to arrange the HDR brachytherapy. This I declined, as I would prefer a radiation oncologist who practised much nearer to my home as after the HDR brachytherapy treatment, I would need to undergo about 30 doses of x-ray radiation over about six weeks. This assumed that I would decide on HDR brachytherapy, which was a decision not yet made.

At about this time, which was six weeks or so after my second post diagnosis visit, I had reason to contact the private clinic that was named as now doing HIFU, only to discover that they were ‘no longer using HIFU’. No explanation was forthcoming. I understand that at least two of the other doctors doing the HIFU treatment in Sydney rent the device from the manufacturer (a different brand from the private clinic above) for the procedure. The cost of the procedure was about A$14,000 of which about 75% would be funded by Medicare and my own private health insurance fund. The private hospital fees were an additional A$4,000.

Chapter 26.

A Third Urologist enters the Picture

I discussed my next possible move with my wife, who had years of experience as a scrub nurse working with the best surgeons and urologists at Sydney’s leading private hospital. She named two specialists who both had HIFU experience at the hospital and were at the top of their profession. She suggested that I get my general practitioner to refer me to one of these two men. Lo and behold! One of them had the same names as my schoolboy professional cricket coach. The coach, who had spent twenty years as a top leg-spin bowler playing County cricket in England, was a huge man who had fingers like bananas. In fact, he was the only man I have seen who could hold three cricket balls (the size of large apples) upside down in one hand! When he ran in to bowl (a type of pitch!), the ball was completely invisible due to the size of his hand. Guess which specialist I chose? The cricket coach’s namesake. A referral was obtained and the appointment arranged.

I was in for another shock. When ushered into his consulting room, I was surprised to find Dr T to be a smallish man, just the opposite in size to my former cricket coach. However, I took to him immediately, due to his quiet, but confident manner, and his ability to impart quality medical information in a straightforward and fully understandable way. After reviewing my pathology records, hearing of my interest in HIFU and PBT, and asking me numerous questions about my urinary flow etc., he suggested the following course of action:

He concurred with Dr L’s view that I might do better than HIFU, by having High Dose Brachytherapy followed by x-ray radiation.

He wanted to do a urine flow test to determine how completely I emptied my bladder.

Dependent on the results of the flow test, he might undertake a transurethral resection of the prostate (TURP) to improve prostate flow before the radiation treatment might begin.

After a three months healing time after the TURP procedure, I would be ready for the HDR brachytherapy and subsequent x-ray radiation.

The urine flow test was scheduled for the following week and I reported to the hospital after drinking the requisite amount of water before arriving. The test equipment measures the volume of urine released from the body, the speed of its release and the length of time it takes for its release. It is very simple test requiring you to urinate into a large funnel that collects the urine in a flask that is on a weighing scale. It sends this data to a computer which prints out a report. The test, called an uroflowmetry test, is over in a few minutes. Dr T was able to advise me that my flow was below par and as such I should undergo the TURP procedure as soon as it could be arranged. A fortnight later, I returned to the hospital to have the TURP operation. It was certainly a more involved procedure than the simple uroflowmetry test.

The TURP procedure calls for removal of tissue from the prostate to improve the urine flow. It can also be used in some elderly or frail men to remove (large) parts of the prostate instead of undergoing a more demanding radical prostatectomy. The procedure calls for the insertion of an instrument called a resectoscope though the penis and urethra into the prostate. The instrument is about 12 inches (30cm) long and one-half inch (13mm) in diameter. It contains valves that control irrigating fluid, a light and an electrical loop that cuts tissue and seals blood vessels. The wire loop is guided by the surgeon so it can remove the obstructing tissue one piece at a time. The pieces of tissue are carried by fluid into the bladder and flushed out at the end of the procedure.

The procedure is colloquially referred to as ‘having a re-bore’. The literature reports that a number of side effects could follow the re-bore: - these include bleeding after the operation and retrograde ejaculation – most men are able to have erections and orgasms after the surgery. However, they may not ejaculate, because the bladder neck is removed along with prostatic tissue. This causes the ejaculate to collect with urine and pass out in the next urination.

In my case, the procedure was green laser-based and somewhat different to the above. The tissue, that was slowing the flow of my urine, was burned away by the laser. This resulted in far less bleeding and is well suited to people, like myself, who are on anti-coagulation therapy. A side effect that I experienced was a need to go to the toilet urgently and frequently to urinate. As the weeks passed, this condition became less and less of a problem. There was also a little blood in my urine for some days after the procedure.

A follow up visit was made to Dr T some weeks later to check my progress after the TURP and to firm up a visit to his recommended radiation oncologist, a Dr W. However, I still had not fully accepted that I would follow through with his recommended treatment. I thought that I would meet Dr W. and see what he had to say. It was now mid-September 2012.

I had some concern about the cancer cells in my prostate that were multiplying as every day went by and might at any time try to escape through the prostate wall into the lymph nodes and/or seminal vesicles. It was this human trait of wanting to be rid of the cancer there and then, raising its head again.

I Start Androgen Deprivation Therapy

After a discussion with Dr T, I asked the doctor to prescribe Zoladex®, which is an androgenic drug therapy (fully described in Part 2 of this book), which would keep the cancer cells starved of their food - testosterone and its more dangerous variant, dihydrotestosterone. Zoladex® comes in the form of a syringe that sees the Zoladex® injected below the skin of the abdomen, where it leeches into the bloodstream over three months. As my wife, Pam, opened the package, I noted the needle to be very sizeable. In fact, I had never seen a bigger one for use with humans!

I asked her to do the injection and she agreed. I further, asked her to carefully read the instructions on how to operate the syringe, as it had a complicated-looking blue safety device on it. I lay down on the bed with my belly exposed and Pam with the needle poised. After the necessary sterilisation of the injection zone with a sterilizing agent, in went the needle. Then the fumbling started. She could not get the safety device released, so that the syringe contents could be emptied into my torso. Eventually, I had to hold the syringe whose needle was more than an inch into my body so that she could collect the instructions that were on the table 15 feet or so away. After a quick read, the safety device was released and the Zoladex® started flowing into my system. A rather funny, but painful experience. I made sure that the next injection which was due in mid-January 2013 would be less painful and less hilarious.

Chapter 27.

Proton Beam Therapy Re-Visited

I had established that it was possible to have proton beam therapy at two centres, Loma Linda University Medical Centre (LLUMC) outside Los Angeles, USA or the National Cancer Centre (NCC) in Seoul, South Korea. My friend John had fully acquainted me with his Loma Linda experience and I had received a package of information from KMI International Inc. KMI facilitate matters for international patients wanting to attend treatment at the proton beam centre at the NCC in Seoul. I thought that I would request quotations from both hospitals and complete application forms. This included making copies of my histology reports from the pathologists as well as providing each centre with the ‘negatives’ of my bone scan and CT scan, which showed no signs of prostate cancer being metastasised outside of the prostate gland. Both proton beam centres only treat prostate cancer patients with localised cancer (confined to the prostate gland itself).

The quotation came in from Loma Linda. It was US$85,000 for treatment only. Accommodation could be arranged by them close to the centre, but would be for my account. Due to it being in a semi-rural setting a hire car would be needed for the nine weeks stay (39 treatment days, plus three days for the initial testing, set up, treatment plan development, etc.). Of course, I would want my wife, Pam, to accompany me so overall, I was looking at no change out of US$100,000. At my friend John’s insistence, I had been in contact with Bob Marckini, who runs the Brotherhood of the Balloon support group for the alumni of the proton beam centre at LLUMC. I also downloaded his book. It is called “YOU CAN BEAT Prostate Cancer and You Don’t Need Surgery to Do It.” An excellent read and it’s very informative. Bob was very generous with his time and answered numerous questions that I had about PBT and the LLUMC.

Before I had my first consultation with Dr W, I heard back from Korea. I was medically acceptable to them and if I accepted their quotation of US$56,000, they could schedule a treatment spot for me within about three weeks. Their quotation included 39 treatment sessions, a three-day session of initial tests, set up and treatment planning, accommodation in a two-bedroomed luxury apartment in downtown Seoul, a driver to take us to and from the hospital each day, a cell phone (with 300 hours of free air time) to contact their English-speaking concierge in the case of need, and a free continental breakfast each week day. All we had to pay for was the air travel, other meals, food and the cost of sightseeing. The two questions were, did I really need PBT and where the Koreans the ones to deliver it?

Chapter 28.

Enter the Radiation Oncologist

It was time to see Dr W, the radiation oncologist. At least I knew before seeing him that I had one option approved and that was PBT at the NCC in Korea. Dr W was very thorough. He explained that I would have about 20 hollow tubes inserted via a template into my prostate via the perineum area. Radioactive-tipped needles would then be introduced via the hollow tubes into the prostate. These would be left in place for some minutes (can’t recall the exact time), then withdrawn and automatically placed in a lead-lined storage safe. The template and hollow tubes would remain in situ over-night (a very uncomfortable night I’m told). The next morning, the needles are re-inserted and remain in situ for a similar time period, before the procedure is completed.

I was to start the x-ray treatment a week after the brachytherapy procedure. Dr W uses an IMRT system which definitely limits the x-ray exposure to the healthy tissue adjacent to the prostate. In six weeks, after the delivery of 28 fractions, I would be as right as rain with my PSA expected to drop to negligible levels over the coming months. The cost of the procedure was to be A$33,000 (then US$31,350). (A$13,000 out of my pocket with the rest chargeable to my health insurance fund and Medicare). They also offered a new type of gel injection for about A$3,000 which would separate the prostate from the rectal wall, which would just about prevent any rectal radiation damage. See Chapter 8.2 for details of this gel. I have subsequently found out much more about this gel, called SpaceOAR®.

It is suitable for photon and proton radiation techniques. If I had been more familiar with its benefits, I would have insisted on it being included in my radiation treatment. Dr W didn’t particularly like my ongoing interest in proton beam therapy. He tried his best to convince me that the Bragg Peak Effect provided by proton radiation was not as controllable as I understood and the result that I would obtain might be sub-optimal. However, he did schedule me to undergo the HDR brachytherapy procedure for the second week in January. (The healing process from the TURP had to be completed before radiation treatment could commence). A final reflection; the bill for almost an hour consultation was a very low A$165, which surprised me. My cynical streak is emerging again. Perhaps, the treatment cost would cover this low initial consultation fee, many times over. We will hear more from or about Dr W. soon.

Chapter 29.

Enter the Case for Hyperthermia

A few days after the October consultation with Dr W, I received a phone call from John. He told me that he had coffee with an old friend, whom he had not seen for a while, who had six months earlier returned to Sydney after having had prostate cancer treatment in Germany. He went on to tell me that his friend, Bill, had another younger family friend (Brian) who had more recently gone to the same clinic just outside Munich to have the same treatment. I had been aware that hyperthermia treatment for all types of cancer had been happening in Germany for years, and I had looked into the work being done by Dr Douwes at the Clinic St Georg at Bad Aibling, near Munich. I was also aware of the work being done by Dr med Peter Wolf at his clinic in Hannover.

I downloaded Dr Wolf's book "Innovations in Biological Cancer Therapy" and carefully studied its contents and read the many research papers, which back up his various treatment protocols. Both these clinics treat prostate cancer with heat radiation and work on the premise that cancer cells are unable to survive prolonged heating to above 42° C (108° F). This is due to the tumour's poor vascular network not being able to dissipate the induced heat, as is the case with healthy tissue with their superior vascular structure. The heating of the cancer cells also leads to the release of heat shock proteins (HSP) by the cancer cells. The HSP make the cancer cells far more vulnerable to attack by both one's own immune system and low dose chemical or biological agents. Unfortunately, Bill left on a four-week business trip to Thailand the day after meeting John, so I was unable to catch up with him face to face. A few emails back and forth made hyperthermia more promising to me. A day or two later, I received an email from LLUMC saying:

“Congratulations. You have been accepted to undergo proton beam therapy with us. A time slot is expected to be available in forty-five days” (early January 2013).

Gee – I now had two options from which to choose. I went back to LLUMC and ask for a listing of Australians and New Zealanders that had PBT at Loma Linda and who would be willing to give me feedback on their experience. The list that duly arrived by email was much longer than I expected and I made email contact with a few people who lived in Sydney or its surroundings. Every reply was very positive and endorsed what John had told me previously.

At this time, I also emailed KMI for details of any Australians or New Zealanders who had PBT at the NCC. I received contact details for an Australian called John, and a New Zealander called Derek, who had sold his house and downsized to help pay for his treatment in Korea. Both have testimonials on the http://www.protonkorea.com web site. I made email contact with John, who lives almost 1500 miles north of my home, which prevented a face-to-face meeting. He was very generous in answering my many questions, both about the treatment and about living in Korea for 10 weeks or so. He completed his PBT treatment at the NCC in March 2012, and at the time of last contact, he was still as positive as ever about the treatment, his recovery and every other aspect of his Korean experience. It was interesting to note that John had received 28 radiation treatments, rather than the standard 39 sessions offered to all international prostate cancer patients at the NCC. This called for the delivery of a slightly higher daily radiation dose to compensate for the fewer treatments.

After a bit of ‘to-ing and fro-ing’, I obtained the email address of Brian, who had undertaken a course of hyperthermia at the Clinic St Georg in Germany. After a few emails, at last I had an opportunity to speak with him over the phone. This lengthy discussion suggested to me that hyperthermia was a really viable option for me. Brian had had his treatment some 6 months previously (not long after Bill’s treatment). His treatment program was as follows:

Thursday afternoon - Arrive at clinic and have general examination and blood tests.

Friday - Undergo the three-hour transurethral treatment followed by being placed on a drip.

Saturday morning - A further drip during the morning (then left the clinic for the weekend).

Monday - Second three-hour treatment.

Tuesday - further drip.

Wednesday - discharged at noon.

His treatment involved a probe being inserted via the urethra into the region of the prostate. This probe was activated by radio-frequency energy to heat the prostatic tissue to 47 – 48° C (117° F) with the temperature being closely monitored by a temperature sensor built into the probe. The procedure was done under local anaesthetic and was painless. The drips he had, included a series of chemical and biological agents designed to stimulate his immune system to attack the heat shock proteins that had 'put their hands up' after being subjected to the two sessions of heat. A six months course of Androgen Deprivation Therapy was also commenced on his arrival for treatment.

The clinic found it possible to offer him a somewhat Spartan room 'in house' for the duration of his treatment. The total cost of the treatment was around A$10,000 (US$6,800 today). His input, together with the research data presented to me by the clinic convinced me that hyperthermia was a cost-effective solution to my prostate cancer problem. It appeared to have fewer side effects than almost all other treatments. One of their research papers[1] reported:

Patients at the earliest stage of prostate cancer, (stages Type l, NO, MO) 16 men out of 16 (100%) had complete remission. At five years post treatment, all of the 14 surviving men were still in complete remission. The two that had died in the interim, died from conditions other than cancer. Patients with early stage disease, (T2 a-b, NO, MO) 32 men out of 32 (100%), also had complete remissions.

The size of the study was small, but obtaining 100% complete remission at 5 years can't be ignored.

There were three other questions regarding hyperthermia that I needed answered. Firstly, the Israel-made machine, used by the clinic, appeared to be out of production, with no apparent replacement available. Secondly, the transurethral hyperthermia (TUH) treatment appeared to be only available in Germany and Austria. Whole body hyperthermia clinics exist in many countries, including Australia. If the TUH treatment was so good, why had it not been adopted elsewhere? Thirdly, the US FDA had approved the use of microwave hyperthermia more than ten years ago, but only when it was followed by radiation therapy. Why was radio frequency induced-heating not considered for approval? I intended to find answers to these questions before making a final commitment to attend the Clinic St Georg. The clinic asked me to forward my prostate cancer medical records to them for their review. A few days later, I was disappointed to receive an email from them which stated: “Regrettably, we are NOT able to accept you as a patient due to the fact that you have had a TURP operation, and the resultant scar tissue is not compatible with our treatment regime.” I had pretty well concluded that transurethral RF hyperthermia was the way to rid myself of my prostate cancer.

Subject to satisfactory answers to the three questions posed above, I was ‘almost on the plane’ to a part of the world that I know well and very much like. (In the last month of my working career 13 years ago, I led an Australian Trade Delegation to Munich, Darmstadt and Frankfurt. We spent a week staying in a village near Bad Ailing and very much enjoyed the hotel there. Visiting the Max Plank Institute, the Fraunhofer Institute and other world class research centres in Munich on the business trip was also a great experience. The hotel had to rush in new supplies of our favourite red wine, Robert Mondavi Cabernet Sauvignon (Californian Napa Valley) from their suppliers!

As I still had not given up hope for a hyperthermia solution, I contacted Dr med Peter Wolf’s clinic in Hannover, pointing out that I had been rejected for transurethral RF hyperthermia treatment by the Clinic St Georg. The Dr Wolf clinic confirmed that the scar tissue problem would not allow them to do the transurethral RF hyperthermia treatment either. They were of the view that they could still assist me in my fight against the cancer. They proposed the following alternative treatment program:

“You will receive daily 2 hours local-regional hyperthermia and once per week whole body hyperthermia, which takes about 3.5 hours. During these treatments you will receive the individually prescribed intravenous infusions, and you will orally take daily the additionally prescribed medication.”

The cost of the three-week treatment as an out-patient at the clinic was to be Euro 3,500 per week, plus Euro 1,500 to 2,000 for pharmaceuticals during the treatment and for three months’ supply for use after the clinic visit. Their quotation also included the following:

“Due to our many years of therapeutic experience, we have come to believe that only a combination of orthodox medicine and the broad spectrum of the

alternative medicine, the way we apply it, offers promising ways in cancer therapy. This opinion is shared by a growing number of university experts in cancer therapy. Today, they also see the necessity for personalised and individual treatment with medication and food supplements. It is important, that the chosen therapies and their respective aims are complementary in order to increase the success of the overall therapy. This is the reason why our complementary therapeutic offer is in line with traditional methods and creates a receptive and supportive environment. Our therapy methods are designed to work on different levels:

Destroying tumour cells

Strengthening the immune system

Stabilisation of the detoxification processes of the metabolism

Optimisation of the anabolism

Increasing the quality of life

Creating a supportive environment in handling the disease."

After reading Dr Wolf's book referred to earlier, I felt that his approach to cancer treatment was likely to lead to a good outcome. However, I was interested in having transurethral hyperthermia, as reported by Dr Douwes at the Clinic St. Georg, that offered me an almost certain prospect of 100% cancer remission (admittedly based on a small study sample size). So regretfully, other hyperthermia treatments were not for me.

A little more detail on Brian's prostate cancer history before he had the hyperthermia experience:

He was 51 when his PSA jumped from 4.2 to 4.7 over the period of a year. His urologist suggested a biopsy, which was subsequently done. None of the 10 cores showed cancer. He missed a PSA test the following year probably due to complacency after he had received the 'all clear' after the biopsy. At 53, he had another PSA test done and he was shocked to see his PSA result come in at 7.0. This time his urologist undertook a 25-core biopsy which sure enough found cancer. It was a Gleason 7 (3+4). His urologist suggested a radical prostatectomy and he was booked in to have the surgery.

Whilst he was waiting for the operation with some fear, dread and specific concerns about the threat of incontinence and erectile dysfunction, he received an email from a fellow prostate cancer sufferer, who suggested he check out hyperthermia at the Clinic St. Georg in Germany. Unfortunately, he put the email aside, without fully researching it at that time. Apparently, he decided to undertake a herbal-based treatment that had shown promising signs in a USA university study. After a few months he abandoned this treatment, when his PSA continued to increase. When it reached 14, he again elected to have the radical prostatectomy. Whilst he was awaiting the operation and still harbouring concerns about the possible side effects, he again 'found' the email about the Clinic St. Georg. A few days of concentrated research resulted in him again cancelling his surgery and electing to have the transurethral hyperthermia treatment done in Germany.

On his return to Australia in February 2012, Brian had two 3D Power Doppler Ultrasounds done over a period of a few months. They showed the prostate had shrunk by 25%, and confirmed that the prostate was effectively dead with no sign of the tell-tale cancerous vascularity remaining. It did detect a number of prostatic stones that had formed from prostatic gland secretions into pearl-like calcified deposits. These stones were unlikely to be problematic.

Chapter 30.

How Do You Get to a Final Treatment Choice?

I was scheduled to have a Prostate Ultrasound Volume Study at the radiation oncologist’s rooms in Sydney, in preparation for the high dose brachytherapy treatment due to be done in January 2013. The Study was to be done on the 27th November. It was getting down to the wire as to me possibly having brachytherapy. It was time to make a decision: HDR brachytherapy or Proton Beam Therapy. I had discarded other treatment types.

It would have been helpful if I had a worksheet or check list that I could go through to try to help me decide. Whilst researching material for this book, I came across such a worksheet designed by Dr John McHugh, an urologist and prostate cancer sufferer, from Georgia, USA. He is also the author of a best-selling book on prostate cancer called “The Decision: Your prostate biopsy shows cancer. Now what?” He also has a very extensive web site, a regular newsletter and a blog on prostate cancer. Access his web site via Appendix 3. His worksheet did not exactly contain all the questions that I would find appropriate to my HDR brachytherapy versus proton beam therapy conundrum and, at the time I had to make this decision, I was not aware of Dr McHugh or his worksheet.

The issue became one of trying to weigh up the likely side effects and possible recurrence of the cancer after each form of treatment. My research led me to believe that proton beam therapy offered the best outcome on both, fewer side effects and less likelihood of a recurrence. I must say, that at the time I made the decision, I was not thinking with absolute clarity as I was still under the ‘let’s get rid of the cancer now’ syndrome. However, the decision to go with the vastly more costly PBT had been made and I now had to make a decision between going to Loma Linda in the USA or to the NCC in Seoul, Korea.

My research into the NCC revealed it was regarded as one of the most advanced cancer treatment centres in the world. It was equipped with the very latest technology and the IBA brand PBT system and its cyclotron were relatively new. So, there were no concerns from a technical stand point. The people at KMI were very easy to deal with. I should explain that Curtis Poling, who runs KMI and his daughter Andrea Poling, are based in the USA. Curtis had previously been treated at Loma Linda for prostate cancer. Emails to Andrea were answered very promptly and contained all the material or answers requested. Email discussion with John from Central Queensland, as a past patient at the National Cancer Centre, was also very supportive of a Korean solution.

I came across a fellow Australian who previously had prostate cancer treatment at one of the regional proton beam centres in Japan. He had hired a translator to work with the non-English-speaking medical staff at the facility. Whilst, he achieved a good outcome, he would not go through that again, purely due to the language barrier.

It was clear that language would not be a significant problem at the NCC as the head of their proton beam facility, Dr Cho Kwan-Ho, had spent 13 years practicing in the USA. Most of his medical colleagues responsible for treating other types of cancer were also trained in the USA. KMI’s presence in Seoul was via Wendy Lee, who is a charming (and attractive) young lady who had done under-graduate studies in Australia. She acted as a concierge, meeting international patients at the airport, introducing them to the NCC staff, arranging the daily driver, taking them to the superb apartment complex (DMC Ville) and to the local supermarket located in the World Cup 2008 stadium about a mile from the DMC Ville in the centre of high tech Digital Media City. All this would cost US$55,900. With the then favourable US$ to A$ rate of exchange, the all up cost, including economy airfares for the 10-hour flight, was going to be around A$55,000.

The LLUMC quote was US$85,000 (45 treatments sessions including medical costs only). With air fares to LA and back, a hire car and accommodation costs added, we would see no change from US$100,000 (then A$95,000). Whilst I had every confidence that the Loma Linda treatment plan was the best available, the extra A$40,000 had to come out of our pockets, with no re-imbursement from our health insurance fund.

Chapter 31.

The Decision is Made: It’s Proton Beam Therapy in Korea

I have travelled to the USA numerous times and have really enjoyed the country and its people. Similarly, I have visited Japan many times and have experienced Tokyo and many regional centres. I was interested in sampling the Korean culture and comparing it to that of Japan. So, the die was cast: Pam and I decided that we would accept the KMI offer to have treatment at the National Cancer Centre in Seoul and made steps to arrange a date for the start of treatment. They were delighted to hear we were coming and set down the 7th January, 2013 as our first day at the NCC.

One thing that did worry us was the weather in winter in Korea. We live adjacent to the ocean in Sydney and have an average temperature in January/February of about 30° C (86° F) with some days getting up to 40° C (104° F). Seoul on the other hand, had January/February temperatures down to as low as minus 25° C (minus 13° F) and that’s ignoring the snow, frozen footpaths, chill factor, etc. Unfortunately, as we were to travel in peak holiday season, we could not get any special deals on travel and finally booked two return economy tickets on Asiana Air, one of the two Korean-owned airlines that fly to Australia.

I had one last task to do before preparing for our Christmas season and that was to communicate with Dr W regarding my decision not to proceed with the HDR brachytherapy treatment. I tried to contact him unsuccessfully by phone over a few days, and for some reason did not leave a message. After the third or fourth attempt, I did leave a message to the effect that I would not be proceeding with my treatment with them and for them to cancel my Prostate Ultrasound Volume Study appointment. I added that I had decided to undergo proton beam therapy in Korea. I concluded the call with an apology for not following through with treatment with him and thanked him for his input up to then. A few days later, I was surprised to receive, a copy of a letter addressed to my (third) urologist (Dr T) by Dr W. He said that it was a little sad that I had been persuaded that proton treatment is more effective than brachytherapy. He went onto state that looking at proton therapy versus other external beam radiation treatments, showed that proton beam treatment was no more effective than other radiation methods, and on par with surgery. It was certainly not shown to be better than their brachytherapy program. He concluded the technical part of the letter with two statements:

"...it is a single fraction each day from one direction only and as such there are certain radiobiological issues that imply that this is a less than ideal way of delivering such treatment. ……… he does unfortunately run a relatively high risk of rectal complication that he will need to have dealt with on his return."

He concluded by wishing me well. He had every right to write this letter. However, I was a little miffed when I received it. His comment about me receiving a single daily fraction is not quite right as one gets two exposures, one through each hip per session. The newer pencil beam scanning PBT systems irradiate different parts of the prostate sequentially during one session, so his comment is clearly incorrect, when considering the very latest systems. He is considering PBT versus IMRT or RapidArc® in which multiple fractions attack the target from different directions during each session. His comment about the relatively high risk of rectal complications has some merit, as I did experience minor rectal bleeding some six months after the treatment concluded which persisted for eight months, until mid-2014. More details on this matter later in the book.

I called the hospital pathology department who last had my histology slides from my prostate biopsy only to be told that I couldn't have them! The NCC insisted that I bring them with me to Korea. A phone call to my first urologist saw him spring to the rescue. They were released to him and I was able to collect them and pack them carefully into my suitcase (the slides are very thin glass)

Passports and visas were sorted out and we were just about ready to go. All our heavy overcoats, gloves, long thermal underwear, beanie's, etc. were aired ready for use in what promised to be a very challenging environment for us Aussies (who migrated to Australia from South Africa in 1979).

Chapter 32.

The Pre-Treatment Program in Korea

As Pam and I approached the Sydney International Airport, the mercury hit 38° C (101° F). It was the warmest day of the Australian summer. We were soon on our way on our Asiana Airlines non-stop flight to Seoul. The service on board was exemplary, as you would expect from an airline that had been voted the best international carrier a year earlier. Just prior to landing, the captain came on over the intercom and said it was a very cold evening in Seoul – in fact it was minus 20° C (minus 4° F). Snow and ice were everywhere.

A quick passage through customs and immigration saw us met by the KMI concierge, Wendy Lee and the driver, Mr Chow. We were soon on a snow-covered highway speeding towards our accommodation at the DMC Ville apartments some 45 kilometres away and just 8 kilometres from the Seoul City Hall. We were soon settled into our two-bedroomed, two bath-roomed luxury apartment that was to be our home for the next nine weeks or so. Wendy said she would meet us at 10am the next morning (Monday) to take us to the nearby giant HomePlus supermarket under the World Cup Stadium to buy food and groceries. We completed our continental breakfast in the breakfast room of the complex, which is only available to international visitors to Korea, before Wendy collected us for our first Korean shopping experience.

HomePlus was huge and of course everything was in Korean. An hour later, we went through the checkout with a full trolley and were presently surprised at the value received. It was perhaps two-third of Australian prices or even less. Wendy dropped us off at the apartment and said she would return at 9.00am the next morning to take us to the NCC which was 25 kilometres away towards the North Korean border. The centre of Seoul is 55 kilometres from the Demilitarized Zone between North and South Korea. We spent the rest of the day settling in and exploring the 200-apartment complex. Its facilities include an indoor golf driving range, a putt-putt course, a 25 metre, heated, under-cover swimming pool, squash courts, children's play room and a very large, fully-equipped gym with an English-speaking instructor. As a keen golfer, I thought that I would be able to work on my golf swing whilst I was in residence!

At 9.00am sharp, Wendy and Mr Chow met us in the foyer, where we were joined by Jan, Henry and Henry's wife, Helen. Henry was into his 7th week of treatment whereas Jan was, like me, about to start treatment. Wendy drove Jan, Pam and I to the National Cancer Centre, with Mr Chow driving Henry and Helen there via a very icy and snow-covered freeway. The 30-minute trip was completed without incident and we arrived at the National Cancer Centre. It was a huge multi-storey hospital that looked ultra-smart and modern. We parked in the underground car park adjacent to the Proton Beam Centre and went into the equally impressive Centre to start a day of briefings, and various tests. As we entered the Centre, I noticed a large picture of the NCC with the caption below it stating:

"THE BEST CANCER TREATMENT CENTRE IN THE WORLD."

I thought to myself, that's very comforting.

After completing various forms and handing over my biopsy slides, and CT scan negatives, I had my weight and blood pressure checked. My blood pressure was higher than normal, perhaps due to underlying sub-conscious anxiety, as I was about to start treatment. I was given an injection of a radioactive tracer, to prepare me for my afternoon bone scan. Also, a blood sample was taken to check my PSA and testosterone levels. Earlier, we had noticed a noticeboard at the control room level of the PBT Centre that contained the photos of international patients that had recently completed PBT treatment at the facility. The photo of John from Central Queensland and his wife was included. Also included was a photo of an eight-year-old girl with her parents. She had completed a course of 56 treatments for a brain stem tumour. I learnt later that she would almost certainly have died, if it was not for her PBT treatment.

We were ushered into a VIP private ward on the 11th floor of the hospital to await our 1.30pm appointment with Dr Cho, who was the head radiation oncologist for lung, head and neck, central nervous system, prostate cancer, stereotactic radiation and PBT at the Centre. After a while we felt a little peckish, so we went across the main road to a Paris Baguette pastry shop that we had spotted as we arrived at the NCC. We had been told about this chain of 500 shops that sell the most delicious cakes and pastries outside of Paris itself. The view from our 11th floor waiting room was towards Seoul. Whilst it was a little hazy, we could see the scope of the city of Islanding, one of the fifteen or so satellite cities that surround Seoul. Twenty to thirty storey apartment blocks were everywhere.

Pam and I were escorted into see Dr Cho. He thanked us for selecting his facility for treatment and said we had made the right decision to have PBT as he was convinced it was very effective and carried minimal side effects. He did say that I might possibly have some rectal bleeding some six months down the track, but that it would soon pass and shouldn’t cause me any further trouble in the future. He explained that at each radiation session, a balloon-like catheter would be inserted in my rectum and it would be filled with water. Its purpose was to press the prostate forwards so that it would always be in the exact same position. He also indicated that I should drink 500mL of water at least 30 minutes before each radiation session. The final question to be settled at the meeting was the number of radiation sessions I would have. I had been quoted for the standard 39 sessions, but I was aware that Koreans only receive 28 fractions. John from Queensland also only had 28 treatments. At that time, we had no real idea how we would enjoy Korea and felt that 39 sessions, together with a number of public holidays, would see us there for 10 weeks, which might drag on somewhat, if we were not enjoying the non-medical side of the visit. Dr Cho indicated that 28 fractions at slightly higher dosage would be more than adequate. They are inclined to do the 39 sessions as that is what the USA and European competitors offer! He also indicated that I would receive a small credit for the accommodation saving, at the end of our stay. So, 28 treatments it was to be. I could hardly wait to get started and attack the cancerous cells multiplying in my body. Having said that, the Zoladex® ADT effect had well and truly kicked in, with my testosterone levels and PSA way down. My libido was also close to non-existent, and I told my wife that ‘men were starting to look attractive’! Dr Cho suggested that I have my second Zoladex® injection, when it was due in mid-February.

He indicated that they were well-pleased with my medical records and that my treatment would start on the following Monday. He gave me a full medical including a DRE. He found my prostate to be pressing against my rectal wall but with no irregularities. Pam and I were to meet with Dr Cho each Tuesday until my treatment was concluded. I found him very engaging and felt that his team would deliver me an optimal outcome.

Pam was ushered back to the VIP private room, whilst I was taken by Ms Hyun Ah Lim, their international proton therapy coordinator, to the pathology station to give them a urine sample. As I was a little dehydrated, it was a bit of a challenge. I emerged from the sampling room with the capped bottle of urine in my hand. I was in trouble, as I should have opened a small sliding opaque window and placed the sample on a shelf. Surprisingly, as I finally placed the sample bottle on the shelf, another opaque door opened and a gloved hand removed the sample. By the way, Ms Lim spoke reasonable English.

Following the CT bone scan, I was met by Wendy, who had received our treatment time schedule. The first session was to be at 3.15pm on the Monday, thereafter at 10.30am until the 24th January, when I would move into Henry’s time slot of 10am. As I moved into the radiology department for an MRI scan, I met Jan coming out after his MRI. He definitely did not enjoy the claustrophobic experience. Five minutes later it was my turn. Even with headphones on and with piped music, the 45-minute session had continuous loud noises being propagated by the magnet movements. Half way through the MRI, a contrasting agent was injected via the cannula previously inserted in the back of my hand.

The hard part was placing my arms above my head for an extended period, whilst breathing in and out on command. The MRI is a very important process in the planning of the treatment program with the prostate image being integrated into the daily x-ray set up procedure. After the MRI, I changed into civvies and Mr Chow drove us back to our apartment, arriving there at 5.45pm after a long, but interesting day.

On returning to our unit, we couldn't get our internet working, nor could Pam get the induction hot top or gas stove top to work. The 'engineer' duly arrived at our request, and the internet was soon working. The 'engineer' who spoke no English, showed us where to turn the induction hot top on at the mains and the almost secret gas cock on for the stove. Tomorrow, the CT simulation scans are due, starting at 2pm. Pam said "I'm giving it a miss." Mr Chow, who spoke very little English, but had an ability to make himself understood, and with a great sense of humour, delivered me to the NCC safely on time. We were to learn that punctuality was one of his greatest assets.

On the Wednesday morning, Pam and I explored the local area in the cold (-10° C). We bought two Travel Cards at the 24-hour convenience shop in the complex. These allowed us to travel by train, taxi or bus anywhere in Korea. Travel there is very cheap. We discovered that a taxi from the nearest metro station, which was a mile away from our apartment, cost us about $2. Our exploration failed to find either of the two Paris Baguette shops that we were told were 'only 5 minutes' walk away. There were numerous coffee shops and restaurants within easy walking distance. We were to find that at least 50 coffee chains exist in Seoul. Many were well known Western brands.

On arrival at the NCC, I was again escorted into the VIP private ward, and given a pair of hospital issue turquoise-coloured thick pyjamas to put on without underpants. I was told a nurse would arrive shortly to do an enema, after which I was to drink 4 glasses of water. This was all accomplished and the cannula re-inserted in my hand. They drew black lines on my upper legs, belly button downwards and crosses adjacent to my hip joints. They then produced a probe that had spikes on the end and inserted it up my rectum. It hurt like hell. It was withdrawn after a few minutes and replaced with another probe/catheter that was left in situ whilst the CT scan was completed. I was then transferred to the hospital radiology department in another building where I had another MRI done with another probe (endorectal coil) up my rectum. Fortunately, the MRI took only 15 minutes, by which time I was bursting to pass urine.

On the way back to the hotel, I spotted the Paris Baguette shop. That’s where tomorrow’s lunch was coming from. The Thursday and Friday were free days. The medical physicists and doctors used it for:

Computer treatment planning

Pre-treatment quality assurance procedure completion

Manufacture of the block and compensators to be used on the proton beam delivery system.

The two compensators are made out of a hard-plastic material. They have a cut-out relief in each which is an exact copy of the shape of one half of the prostate. They are used to minimise the radiation to areas beyond the prostate outer wall. The blocks are solid pieces of brass that are about three inches thick with an aperture in them, with the aperture being the exact outline of the prostate as seen from the hip joint. The right-hand block and compensator are replaced by left hand versions as the gantry moves overhead to prepare for the treatment of the other side of the prostate.

By now, Pam and I had mapped out all the places we wanted to visit and the things we wanted to see during our stay. The holiday side of the trip started in earnest. We quickly discovered that Korea was an enchanting place and the people were very helpful and engaging. We estimated that about 20% of the people could speak English, to a greater or lesser extent. You only had to stop on a street corner and look at a map before someone would come up to try to help you. We had a few comical such encounters with people who could speak no English, but were determined to help us. Wearing our thermal underwear, heavy overcoats, gloves, a scarf and headgear, made us more able to cope with the very cold weather.

It became the norm to get back from the NCC at about 11.15am each treatment day, have a hot cup of coffee, put on my thermals and for Pam and I to go sightseeing. Each day, the apartment complex courtesy bus went to HomePlus and did other set trips down town. Every Saturday, it took us to a Costco and HomePlus near the NCC. We were amazed at the shopping loads that people brought back onto the bus. As the weeks went by, we became very familiar with the local bus service, using green, red or blue buses that passed the DMC Ville every two minutes or so. It cost us about 60 cents each to get to town.

We also developed a good friendship with Henry and Helen. Pam joined them most Sundays at a church in downtown Seoul where they were all made very welcome. Jan’s schedule called for afternoon treatment, so we didn’t see too much of him, though occasionally we would spend an hour or so comparing notes about our treatment, at one of the coffee shops across the road from the apartments. A few weeks into my treatment, there was general consternation in Seoul, when the regime in North Korea exploded an atomic bomb. A Sunday trip to the Demilitarised Zone between North and South Korea, was a most interesting experience, but made you aware of the continual threat that conflict could resume between these two countries at any time.

Chapter 33.

My Treatment Begins

On the Monday afternoon, I arrived at the PBT Centre in good time and was shown into a change room, where I put on the requisite pyjama trousers without underpants and waited to be called into the treatment room. There are three beam lines at the NCC with one a fixed line that is used for head, eye and neck cancer treatments. I was escorted into the treatment room by the two medical therapists (one spoke good English with the other not so good English). I climbed up on the flat table, removed my pyjama pants, placed my feet up on a type of immobilization device and waited for the balloon catheter to be inserted and filled with water. This took less than a minute to do and the therapists were clearly well skilled in this procedure. The following ten minutes were devoted to positioning me precisely to the millimetre in the correct position. This involves lasers built into the gantry illuminating the crosses previously marked on each hip joint, horizontal and vertical x-ray extensions coming out of the wall to image you in two planes, computer-guided minor adjustment of the table which together matched precisely the position and size of my prostate.

At this point the two therapists left the room to start the diversion of the proton beam through the radiation probe. I could hear the system starting up as it emitted a low whir, which became more intense as the period of radiation started. The proton beam travelling at 100,000 miles per hour irradiated the prostate for about 90 seconds, after which the system went into standby mode. The therapists returned and the gantry moved through 180 degrees to ready itself to irradiate the left side. The right-hand block and compensator were replaced with the left-hand versions within less than a minute and the same positioning set up was done as for the right-sided entry. The radiation was commenced after the therapists left the room and it was over in no time at all. The rectal catheter was removed and disappeared from view before I could sit up. In fact, I never actually saw it before or after it was inserted all the time I was there. I regained my modesty by pulling my pyjama pants up, climbed off the table, thanked the staff, went to the toilet to do a few running repairs, dressed and was ready to collect Pam and journey back to our apartment. The duration of my time in the treatment room was less than 25 minutes.

This procedure was undertaken time and again. It was totally uneventful, until the good English-speaker was promoted and a new medical therapist joined my treatment team. After a few days as the No. 2 man, it was his turn to insert the balloon catheter. He pushed it in, but didn’t know when to stop. A quick screech in pain from me, made him realise that I was running out of room! He was very embarrassed and even more apologetic. I never had a problem after that.

Weekly meetings with Dr Cho, were pleasant experiences, but uneventful. On the second last treatment day, I had blood and urine samples taken. Yes, I used the sliding door and saw the other door open and the urine sample disappear into a gloved hand. On the 21st February, I had my 28th and last fraction. After the session concluded, I was invited to bang the shield (just like the Rank Organisation shield of old movie fame) outside the treatment rooms to signify the end of my journey. This was followed by morning tea with Dr Cho, his medical therapists, the medical physicists, Ms Lim, Wendy and the reliable Mr Chow. Paris Baguette had provided a great cream cake. Dr Cho again thanked me for selecting the NCC for treatment and presented me with a wonderful certificate confirming my attendance at their facility. He also included a USB which included my medical records which confirmed that I had received 7000 cGy, the agreed dose, at the rate of 250 cGy per fraction.

All I had to prove that I have had the treatment was a circular spot about two inches in diameter on each hip joint. This was ‘sunburn’ caused by the entry of the proton beam at this spot. The next morning Mr Chow drove us out to the Incheon International Airport and we thanked him for his service whilst we had been in Seoul. We had two experiences whilst in his care. One morning, we were on our way to the hospital when we hit some black ice. The car spun through

360 degrees without hitting anything and we continued after a laughing apology from Mr Chow. The other ‘happening’ was the freeway being blocked by South Korean soldiers. We thought hostilities may have started with the crazy North Koreans, who are still technically at war with the South. Apparently, they were on an army manoeuvre. The South Korean people were very perturbed by the Northern Koreans undertaking two atomic bomb tests whilst we were in Seoul. The Demilitarised Zone is only 55 kilometres (34 miles) from Seoul and only 30 kilometres (19 miles) from the NCC. Our one-day trip to the DMZ reinforced the threat that the North represent to the South.

Chapter 34.

The Post-Treatment Period

By the end of April 2013, the last of the Zoladex® had left my system and my hormonal state returned to normal. I certainly stopped looking at the men and noticed pretty girls again! My first PSA after my return to Australia was 0.26 and my free PSA was at 5% versus 9% before going to Korea. A subsequent result in June 2014 was 0.22. I had not yet reached the nadir value which according to my doctors, should be reached late in 2015. August 2015 gave a PSA of 0.19. A further PSA test in May 2016 came in at 0.14 which probably will be my nadir value.

In July 2013, the rectal bleeding started. It was only minor, but it was a bit of a shock to have the toilet paper all red for the first time. My general practitioner prescribed a cortisone-based 100ml retention enema to be injected at bedtime each night, but this didn’t make any difference to the small, but regular bleeding. It was early January 2014, when I decided to raise the issue with Dr Cho. He responded promptly to the point that only 2 in 10 PBT patients exhibit rectal bleeding and it appeared that I was one of them. As I take warfarin for an arrhythmia problem, the condition is almost self-sustaining. He suggested that I should get my bowel checked by a proctologist or colo-rectal specialist. This I did and it was found that I had a radiation burn the size of the fingernail of a man’s smallest finger.

The specialist recommended that we wait four months before deciding on one of the three treatments options used for this condition. I went back to Dr Cho at the NCC with a copy of the photo of the offending area. His response was that it would likely disappear of its own accord over time or I could start a course of rectal retention enemas, with sucralfate as the active ingredient. Unfortunately, it is not possible to get sucralfate in suspension in Australia. However, the good news is that the bleeding had almost stopped and I expected it to be completely gone, within a few weeks. (In fact, after a three-month period with no bleeding, it surprisingly returned in July and as of October 2019 it still persists, but only once every 3 or 4 months). Due to unrelated issues, my physician changed my daily warfarin dose for a new blood thinner called Rivaroxaban (Xarelto® - Bayer). It was thought that this change might also alleviate the bleeding problem. (it didn’t - the bleeding continues to be very minor and is completely bearable)

Chapter 35.

Would I make the same Decision Again?

After having researched and written this book, I have learned a great deal more about prostate cancer than I knew when I assessed my treatment options. I was exposed to prostate cancer in the family before my own diagnosis. Even this did not equip me with anywhere near enough information to be able to cope with what outcomes were possible with the various alternative treatments. Whilst I am sure that almost all doctors are well intentioned when they make their recommendations, it's you the patient, who has to live with the consequences of any treatment undertaken. Some people get side effects that nobble them. As reported earlier in the book, I have a friend that did not have a good outcome from a radical prostatectomy. The result was he started to find relief by drinking far too heavily for his own and his family's good.

The simple issue is that men need to take matters into their own hands by intelligently and thoroughly researching the options open to them. Unless they are diagnosed with metastatic cancer which requires immediate action, they have time to weigh up carefully the various options open to them. Remember that prostate cancer, in the main, is a disease that progresses slowly. This leads me to the story that a friend of mine related to me recently.

Rob was about 55 when he was diagnosed with prostate cancer in 2000. Rob continues his story with some comment from me that is in normal type face.

"At the insistence of my general practitioner I had a PSA test 14 years ago. It came back at 460 ng/ml. The GP had already made an appointment with Dr F (a

well-known urologist at a prestigious private hospital) and I went along not really knowing the seriousness of the report. I had no symptoms and was very fit. No point in operating as the cancer had already spread and a Gleason Score of 8. Dr F put me on hormone therapy and said if all went well, I might have 3 to 5 years. (Expletive deleted). After about one year my PSA was down to 1 or thereabouts, but started to rise in year two. Tried various other supplementary drugs which slowed growth for a while, but still on the rise. At about year 5, PSA was 23 and increasing quickly. Chemo was recommended. Not for me said I. I think I would like to see Dr Snuffy Myers in the USA (Dr F had advised me to buy his book. I had done so and followed his diet regimen very closely which no doubt had helped a lot. Meanwhile, I had subscribed to his newsletter). My then specialist (Dr F had flick passed me on - a real hospital pass this one) said it was a good idea and he had another patient go to see him with quite positive outcomes. (Why he didn't suggest it himself is a mystery).

So off to USA and Snuffy. He reckoned for all that my cancer was something of a sheep in wolf's clothing. Came home with a three-month course of Leukine (not available here) to be taken in conjunction with Thalidomide®. PSA down to low single figures. Whoopee. After a year or so on the rise again, so Snuffy says start with Ketoconazol® (meant for treatment of fungal infections). Down it goes again, but side effects not pleasant. As time went by had to increase the dose of Ketoconazol® to double that recommended. Felt terrible. After a year or two, PSA at 28. Back to USA. Scans I had didn't show anything, although clearly the cancer was on the march. He had me get scans in Orlando, Florida. And these showed a lesion in my pelvic area - lymph node. Snuffy sent me back with a DVD of the scan and an instruction to contact Dr K at a large Sydney hospital where I had 40 episodes of IMRT. That was 5 1/2 years ago. PSA now 0.02. Still on Zoladex® and Avodart® (which inhibits conversion of Testosterone into Dihydrotesterone - which the cancer feeds on) still watch diet but not as rigorously. Feel great. Radiation damage to bladder has affected my urination a bit but manageable. Up 3 to 5 times a night, but who cares."

I include this story as a true inspiration to those with a challenging prognosis for their prostate cancer. I also include it as it shows that no matter how dire is the prognosis, much can be done by the patient himself taking the initiative and finding the best medical help available. It may not be on your doorstep. It might be somewhere else in the world. Sure, monetary considerations come into it, but in some cases, it’s your life you are playing with. Rob is still reasonably well more than 13 years after he was supposed to be dead, because he investigated options not initially put forward by his doctors.

What would I do differently, with what I know now, compared with what information I had available to me, when I made the decision to go to have proton beam therapy in Korea?

In essence, nothing different.

I would still have opted to go to Korea for treatment. However, there are a lot of ‘ifs’ that arise.

If I had not had the TURP procedure that excluded me from having transurethral hyperthermia treatment together with a series of biological cocktails to help kill the cancer, I would have opted for that alternative. It was a rapid and inexpensive treatment, which would not exclude me from having almost all other treatments as a salvage procedure.

If I had known more about mpMRI and colour Doppler ultrasound earlier, I would have insisted on having both done. It would have shown up the precise size, position and extent of the tumours in my prostate. This knowledge may have allowed me to consider treatment of these tumours alone by focussed technologies like HIFU or FLA. This may have left part of my prostate active.

If my Gleason Score was 6 (versus the actual 7), I would have gone onto an active surveillance regime, with mpMRI and Power Doppler ultrasound providing progress reports on the tumour growth.

If I had much more knowledge of the effectiveness of the latest radiation devices such as RapidArc® and IMRT, I just might have gone down the treatment course of high dose brachytherapy followed by radiation provided by either of these systems.

If I could have found a top surgeon using the da Vinci® prostatectomy system with an exemplary record of nerve sparing outcomes, I might have gone down that path, as a radical prostatectomy offers better choices should there be a recurrence of the cancer.

If I had not been ‘scared to death’ of having malignant cells growing in my body which I needed killing immediately, I would have gone into far greater depth in my research efforts.

If I had been fully familiar with the SpaceOAR® hydrogel before my radiation treatment, I would have had the rectum sparing injection. In Australia the cost is covered by medical insurance.

However, life is all about the here and now and ‘ifs’ need to be put into their place as a past opportunity, perhaps a good one, lost. Or more likely, perhaps a lesser outcome being achieved.

So, I can confirm that I would again select proton beam therapy treatment at the National Cancer Centre in Korea as the best alternative to suit my unique circumstances. Of course, to select Proton Beam Therapy, without any health insurance reimbursement, puts PBT beyond the financial reach of most families. Perhaps the same can be said of a few of the other treatments considered in this book. The capability of families to access (geographically, financially or medically) any form of treatment is as variable as the human condition. Readers of this book, each with their own circumstances, might feel similarly or opt for a different course of treatment.

I predict that mpMRI together with focal laser treatment will transform the prostate cancer treatment field for low and intermediate risk patients over the next few years. I also predict that the Holy Grail of finding a treatment that offers few side effects and the lowest recurrence rates will be achieved before 2025.

A final word. I have written this book to try to fill in the many blanks that existed in my knowledge of prostate cancer when I had to decide on a course of action. I will be well pleased if I have been able to help even one prostate cancer sufferer. Hopefully, it will be of assistance to many. Much of the material that I have researched for this book has come from discussions with my doctors, fellow sufferers, a host of books read on the subject and by spending hundreds of hours on the internet. I doubt that there is more information available on any other disease than that available for prostate cancer.

In this, the 3rd edition of the book, I have more fully explored the use of diet, nutrition and alternative therapies that I am convinced will be of assistance to many men with advanced and/or metastatic prostate cancer. Some of whom the medical profession might already have given up on. I have changed my diet and supplement program as a preventative measure, to hopefully, keep myself in remission from my cancer. I have also explored in detail, the challenges faced by mCRPC men and looked at twenty-four new developments, out of which a few new improved therapies will emerge.

I have said many times in this book that I am NOT a doctor, and have stressed that it is imperative that you consult your medical team at each and every opportunity so that you can jointly develop a treatment program that optimises outcomes for you. Hopefully, the questions that I have listed in this book, (and others not listed by me) for you to ask your doctors, might lead to you being as well informed as possible as you undertake your fight back to good health.

I feel that my ‘journey’ over 4 continents to find the ‘best’ cure has been a success as far as my treatment is concerned. I thank you for reading this book, and if you are so inclined, refer it to others who might have prostate cancer, so that they might have more knowledge available to them. After all knowledge is power. I wish you well.

THE END.

Appendix 1

Glossary

acidosis

An abnormal condition resulting from the accumulation of acid or the depletion of alkalis in the body.

active surveillance

A management option for localized prostate cancer patients with the intent to intervene if the disease progresses as revealed by regular testing.

adaptive immunity

The acquired immune system that adapts to immunological events.

i.e. it remembers exposure to pathogens that it was previously exposed to. It works alongside the innate immune system to attack viruses, germs, fungi and other pathogens.

adjuvant therapy

A treatment given in conjunction with or shortly after another treatment to enhance its effectiveness.

advanced prostate cancer

Prostate cancer that has spread to neighbouring tissues or to other parts of the body.

alkaliser

A compound that increase the alkalinity of the body to a pH value of 6.4 or higher.

alternative therapy

Monotherapies whose efficacy has not been validated by clinical trials.

anaesthetic

A drug given to stop a person feeling pain. A local anaesthetic numbs part of the body; a general anaesthetic causes temporary lack of consciousness.

androgens

Male sex hormones. The most active male hormone, testosterone, is produced by the testicles. Other male hormones are produced by the adrenal glands.

androgen deprivation therapy (ADT)

A drug treatment that minimises the effect of testosterone in the body. This type of therapy can slow or stop the growth of prostate cancer. Also called androgen suppression therapy.

androgen suppression therapy (AST)

See ADT.

androgen synthesis inhibitors (ASI)

Compounds with characteristics that are likely to provide effective antitumour activity against androgen dependent prostatic cancer.

angiogenesis

The ability that tumours have to develop their own blood supply, which helps them to survive and grow.

antigen

Short for antibody generator. They are molecules that provoke an immune response in the body.

anti-androgens

Drugs which slow the growth of prostate cancer by blocking the action of the male hormone, testosterone, in the prostate.

antioxidants

A class of molecules that are capable of inhibiting the oxidation of other molecules. They occur in nutrients ingested or are produced by the body in the form of enzymes.

anus

The opening at the end of the rectum through which faeces leaves the body.

apex

The bottom of the prostate.

apical region

The area adjacent to the bottom of the prostate.

ATP

Adenosine triphosphate is a chemical compound that breaks down to release the energy responsible for muscle contraction.

autophagy

The natural, destructive mechanism that disassembles, through a regulated process, unnecessary or dysfunctional cellular components.

beta-sitosterol

β-sitosterol is used in herbal therapy, especially for benign prostatic hyperplasia (BPH) in a number of countries. It can have potentially serious side effects.

benign

Not cancerous or malignant.

benign prostate enlargement

Non-cancerous enlargement of the prostate which is caused by a condition known as benign hyperplasia (BPH).

benign prostatic hyperplasia

A benign increase in the size of the prostate.

biochemical recurrence

It is the increase in prostate-specific antigen (PSA) in patients after surgery or radiation. It may occur in patients without symptoms. It suggests that the cancer has re-emerged.

biofilm

A group of microorganisms in which cells stick to each other and form a matrix of extracellular polymeric substance that protect the host.

biomarker

Generally, a measurable substance indicating some biological state or condition. They are known to shed unique biochemicals, including DNA, into the environment as evidence of their presence in a particular location.

bisphosphonate treatment

It assists in the prevention and treatment of osteoporosis, and bone metastasis in patients with metastatic prostate cancer.

biological response modifiers

Interleukin and/or interferon and other cytokines may be given to patients undergoing radiation and chemotherapy to help support the immune system.

biopsy

When prostate cancer is suspected, after a DRE and/or PSA test, tissue samples in the form of rods, are taken from different areas of the prostate, and are then examined under the microscope to see if they are cancerous.

bladder

The organ that stores urine from the kidneys.

bone scan

A nuclear scanning test in which a radioactive chemical is injected, then its path is traced through the body. The chemical concentrates in areas where there is increased bone activity such as areas of cancer, infection or arthritis. Bone scans are not always precise, but are good indicators of cancer cells being present.

boost therapy

The simultaneous or sequential use of a second therapy to boost the overall treatment result.

bovine tracheal cartilage

It is a nutritional supplement that has been claimed to have beneficial outcomes for some prostate cancer sufferers. The cartilage is said to block the formation of new blood vessels which starve tumours of food.

brachytherapy

It is radiotherapy given from within the prostate. Low dose rate brachytherapy involves the permanent insertion of radioactive seeds directly into the prostate. High dose rate brachytherapy involves the temporary insertion of radioactive-tipped needles into the prostate.

Bragg peak effect

The proton radiation increases its energy as it nears its target depth where it releases its maximum energy before it rapidly returns to zero energy.

cancer

Involves abnormal cell growth with the potential to spread to other parts of the body.

cancer anxiety factor

The psychological stress and disposition that develops when a patient is informed that he has cancer.

catecholamines

A class of aromatic amines which includes a number of neurotransmitters such as adrenaline and dopamine.

catechin

Unfermented green teas contain 27% of catechin which interacts with various human genes.

catheter

A hollow, flexible tube through which fluids can be passed into the body or drained from it.

cells

They are the smallest units of life that can independently self-replicate. Cancer cells are abnormal or damaged cells.

chemotherapy

The killing of cancer cells with cytotoxic chemicals. (Cytotoxic means toxic to cells).

clear margin

Also called surgical margin. Usually refers to the visible normal tissue margin that is removed with the surgical removal of a tumour.

clinical staging

It is based on all the available information obtained before surgery to remove a tumour. It may include information about the tumour obtained by physical or radiologic examination. Pathological staging refers to the information obtained by the microscope evaluation by the pathologist.

clinical trial

A trial of a new treatment or drug, conducted by medical researchers on patients who volunteer to take part. These trials are required to be done ethically and in conformity with accepted international principles.

collagen

The most abundant protein in the body and the substance that holds the whole body together. Almost all body cells are surrounded by collagen which provide strength and structure.

collagen digesting enzymes

Enzymes that are produced mainly in cancer cells that are secreted from the cells to dissolve the adjacent collagen and connective tissue.

combined modality therapy

The use of more than one therapy at once, often used for high-risk cancers. Therapies may include surgery, radiotherapy, hormone therapy and chemotherapy.

complementary therapy

It is alternative medicine used together with conventional medical treatment so as to 'complement' the conventional treatment. The alternative medicine is not proven by scientific research.

computerised tomography (CT) scan

An x-ray scan of a part of the body or region that produce tomographic images or ‘virtual slices’ of the scanned area.

conformal radiotherapy (3D-CRT)

An improved type of external beam radiotherapy (EBRT) where the radiotherapy dose is delivered by a number of beams shaped so that the region where they overlap is similar to the shape of the prostate. This minimises the dose to adjacent healthy tissue.

CyberKnife® radiotherapy

Another variant of conformal radiotherapy. The two main elements are the radiation produced from a small linear accelerator and the use of a robotic arm which allows the energy to be directed at any part of the body from any direction. It reduces the radiation dose to normal tissues, with all parts of the cancer receiving the same dose of radiation.

cytokines

A category of small proteins that are important in cell signalling. They are released by cells and affect the behaviour of other cells.

cryotherapy

A method of killing cancerous cells by freezing the tissue.

cystoscopy

A procedure in which an instrument is introduced along the urethra under local or general anaesthetic, to view the bladder and prostate.

cytotoxicity

The quality of being toxic to cells.

da Vinci® prostatectomy system

A robotic system for complex surgery using a minimally invasive approach.

dendritic cells

They are antigen-presenting cells of the immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system.

deoxyribonucleic acid (DNA)

A self-replicating material present in most living organisms. The so-called ‘building block’ of life.

digital rectal examination (DRE)

An examination of the prostate through the rectum wall. The doctor inserts a finger into the rectum and feels the shape of the prostate, for lumps or areas of hardness which may suggest cancer is present.

dihydrotestosterone (DHT)

DHT, as it is known, has 2 to 3 times the affinity to androgen receptors than testosterone. It has 15 to 30 times more affinity than adrenal androgens. About 5% of testosterone is converted into DHT by the body. DHT is a key food source for cancer cells.

Doppler ultrasound

A medical device that makes use of the Doppler Effect to measure and visualise the flow of blood in the prostate.

doubling time

The time taken for the PSA level to double, for example, from 4 ng/mL to 8 ng/ml. It is a measure of how fast the cancer is growing.

down regulation or up regulation

The process by which a cell decreases the quantity of a cellular component, such as RNA or protein, in response to an external stimulus. The complementary process that involves increases of such components is called upregulation.

dry ejaculation

After a radical prostatectomy, a man may achieve orgasm, but produce no ejaculate (fluid). This is because the glands that produce most of the fluid are removed. See also reverse ejaculation. The same condition usually exists after a full course of radiation as the "muscles" of the prostate are killed by the radiation.

EBRT

External beam radiation therapy.

ejaculate

Fluid produced at ejaculation, which contains sperm and secretions from the prostate, seminal vesicles and testicles.

EPIC

A questionnaire called the Expanded Prostate Cancer Index Composite (EPIC) requests the patient to quantify against provided criteria, levels of urinary function, bowel activities, sexual function and overall satisfaction post treatment.

epigenetics

The study of genetic variations that are caused by external or environmental factors that switch genes on and off and affect how cells read genes.

erectile dysfunction

The inability to achieve an erection firm enough for penetration.

erection

When the penis becomes enlarged and rigid during and after arousal.

expression

A wide range of mechanisms that are used by cells to increase or decrease the production of specific gene products.

external beam radiation (EBRT)

X-ray-based radiotherapy given from a source external of the body.

extra capsular extension

Cancer that extends through the capsule of the prostate into the surrounding tissue, as determined from the radical prostatectomy pathology report.

FACT-P

Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a multidimensional, self-reported Quality of Life questionnaire specifically designed for use with prostate cancer patients.

faecal incontinence

Involuntary loss of faeces.

fertility

The ability to naturally conceive children.

fibrin

A white insoluble fibrous protein that coats cancer cells which assists them avoid the immune system’s action.

fiducial marker

A non-radioactive marker (often gold seeds) inserted in the prostate to accurately locate it. It is part of the radiotherapy planning process and helps the accuracy of image-guided radiotherapy (IGRT).

five-year survival rate

A scientific measure to determine the success of a treatment, because it is hard to know if someone is cured or simply in remission. It measures the number of people who are alive after a particular treatment.

focal laser ablation (FLA)

The removal or ablation of diseased tissue by the focused heat energy of a laser.

free to total PSA ratio

The prostate-specific antigen (PSA) in the bloodstream can ‘latch’ onto protein. This is called ‘bound’ PSA. In men with BPH, there tends to be more ‘free’ or ‘unbound’ PSA. This test compares the ratio of unbound PSA to total PSA in the bloodstream.

functional imaging

A form of medical imaging that detects or measures changes in metabolism, blood flow, regional chemical composition, and absorption.

gene

The tiny factors that govern the way the body's cells grow and behave. Each person has many thousands of genes inherited from both parents and they are found in every cell.

gene expression

The process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the product is a functional RNA.

genetics

A region of DNA that encodes function and the molecular unit of heredity.

genotype

The genotype is the part of the genetic makeup of a cell, and therefore of any individual, which determines one of their characteristics (phenotype).

ginseng (Panax variety)

Panax ginsengs are herbs that have pharmacological properties. Their alternative therapy efficacies have not been proven in clinical studies.

Gleason score

A method of grading cancer cells. Low grade cancers with Gleason scores of 2, 3, or 4 grow slower than high grade (Gleason scores 8, 9, or 10) cancers. The pathologist identifies the two most common tissue patterns under a microscope and grades them from 1 (least aggressive) to 5 (most aggressive). The Gleason score is given as two numbers added together to give a score out of 10 (for example, 3 + 4 = 7). The first number is the most common pattern present and the second number is the next most common.

glutamine

It is the most abundant non-essential amino acid in the body. It has therapeutic properties when taken as a food supplement.

grade/grading

A score which describes the level of abnormality of cancer cells, and consequently how aggressive or fast-growing the cancer is likely to be. The most commonly used grading system is the Gleason score, which ranges from 2 to 10 (see above).

gray (Gy)

A measure of a dose of ionizing radiation. A gray is defined as the absorption of one joule of radiation energy by one kilogram of matter.

HDR remote after-loader

A medical device used in HDR brachytherapy which automatically 'loads' the radioactive tipped needles and stores them safely.

high dose rate brachytherapy

HDR brachytherapy is a temporary radiation treatment for cancer and the amount of time that the radiation source is left in place is determined by the radiation oncologist.

high intensity focused ultrasound (HIFU)

It is a highly precise medical procedure that applies high-intensity focused ultrasound energy to locally heat and destroy diseased or damaged tissue through ablation.

homeopathy

A system of alternative medicine in which a substance that causes the symptoms of a disease in healthy people will cure similar symptoms in sick people.

hormones

Natural bio-chemical substances that are produced by one body organ, and travel through the bloodstream to other organs where they influence its physiology and behaviour.

hormone resistance

Prostate cancer cells are dependent on testosterone growth. Withdrawal of testosterone by surgery or by means of drugs is therefore a means of controlling its growth. However, cancer cells may develop which do not need testosterone for growth. The cancer is then said to be ‘hormone resistant.’

hot flushes

A sudden feeling of heat to the face, neck, chest and back that usually lasts for a few minutes, but can continue for an hour. It is brought about by prostate cancer hormone therapy.

hydrocyanic acid

Also known as vitamin B17. Its active ingredient is laetrile.

hyperbaric oxygen

Oxygen delivered at above atmospheric pressure. It can be helpful in relieving some long-term side effects of radiation such as rectal bleeding.

hyperthermia

It is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 43°C or 113°F). There are various formats, such as, regional, transurethral and whole-body hyperthermia.

hypoxia, hypoxemia

Hypoxia: a condition in which the body or a region of the body is deprived of adequate oxygen supply.

Hypoxemia: insufficient oxygenation of arterial blood.

IIEF-15

The International Index of Erectile Function-15 is a standard set of 15 questions that was developed as a measure to detect treatment-related erectile function in patients.

image-guided radiotherapy (IGRT)

Radiotherapy guided by specialised imaging tests, such as CT scans, ultrasound or x-rays. These tests are done in the treatment room just before the patient is to receive daily radiation treatment or during the radiation delivery to compensate for movement of the prostate.

impotence

See erectile dysfunction.

immune system

The system of many biological structures and processes within an organism that protects against disease.

immune-therapeutical agents

They are inhibitors of tumour necrosis factor α.

incidental finding

The discovery of cancerous tissue during other procedures, like a TURP.

incontinence

The involuntary passing of urine (urinary incontinence) or faeces (faecal incontinence).

indolent

A type of cancer cells that grow very slowly.

infertility

The inability to conceive naturally.

innate immune systems

The non-specific immune system or in-born immunity system, is an important sub-system of the overall immune system that comprises the cells and mechanisms that defend the host from infection by other organisms.

intensity modulated radiotherapy (IMRT)

A type of conformal external beam radiotherapy where the radiotherapy dose is delivered by dozens of mini-beams of radiation. IMRT usually results in less radiation dose to normal tissues, whilst all parts of the cancer receiving the same dose of radiation.

intermittent hormone therapy

Hormone therapy which is started and stopped in cycles. Typically, it is continued for several months until the PSA has declined to a low level, and then discontinued. Once the PSA level rises to a particular level again, which might take many months, hormone therapy is restarted. This approach reduces side effects during the 'off ' period.

interstitial

Situated within an organ or tissue.

in vitro studies

Studies that are performed with microorganisms, cells or biological molecules outside their normal biological context. i.e. ‘test tube’ studies.

in vivo studies

Studies that are performed with microorganisms, cells or biological molecules within their normal biological context. i.e. within the body.

IPSS

The International Prostate Symptom Score (IPSS) is an 8-question written screening tool to screen, diagnose and manage the treatment of BPH.

irreversible electroporation

It is a soft tissue ablation technique using ultra short but strong electrical fields to create permanent nanopores in the cell membrane. The resulting cell death results from apoptosis.

Kattan nomogram

A tool that predicts prostate cancer progression outcomes - whether they are for those initially diagnosed or all degrees of the disease to the metastatic stage.

Kegel floor exercises

They consist of repeatedly contracting and relaxing the muscles that form part of the pelvic floor.

lactoferrin

It is a multifunctional protein of the transferrin family and it is a component of the immune system of the body which has antimicrobial activity and is part of the innate defence of the body.

laparoscopic surgery

A surgical method where the operation is performed using small incisions through thin telescopic instruments: A small video camera is inserted. The technique is often referred to as 'key-hole' surgery.

LHRH (luteinizing hormone releasing hormone)

A hormone produced by the hypothalamus in the brain and stimulates the pituitary (another part of the brain) to produce LH (luteinizing hormone). This, in turn, causes the testicles to produce the male hormone, testosterone.

LHRH agonists

Drugs that interfere with the production of LH.

LHRH antagonists

Synthetic peptides that interact with gonadotropin-releasing hormone receptor to elicit the release of pituitary hormones FSH and LH.

libido

Sex drive.

lipids

A group of naturally occurring molecules that include fats, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, and others.

lipid peroxidation

The oxidative degradation of lipids. It is the process in which free radicals ‘steal’ electrons from the lipids in cell membranes.

localised prostate cancer

Early stage prostate cancer which has not spread beyond the prostate.

locally advanced prostate cancer

Cancer which has spread beyond the prostate capsule and may include the seminal vesicles, but is confined to the prostate or nearby tissues only. Type T3c.

locally recurrent

Cancer that has recurred (come back) after treatment, but which is confined to the prostate or nearby tissue only.

lower urinary tract symptoms (LUTS)

Symptoms related to the flow or passing of urine, such as poor stream, frequent urination, needing to get up at night two or more times to urinate, incontinence and incomplete emptying of the bladder. They are often caused by BPH of the prostate, but can also be caused by advanced prostate cancer.

low dose rate brachytherapy

An internal radiation procedure in which radioactive seeds are permanently implanted in the prostate. They lose their radioactive 'charge' after 6 to 9 months depending on the half-life of the radio-isotope used.

lycopene

It is a carotene found in tomatoes and other 'red' vegetables and has been considered a potential agent for prevention of prostate cancer. The US FDA suggests its efficacy is unproven.

lymph nodes

Also known as lymph glands. They are small, generally pea-sized pieces of tissue found all over the body including the groin area adjacent to the prostate. They act as filters for foreign substances and can harbour cancer cells that have spread from the prostate or elsewhere.

lymphocytes

Sub-types of white blood cells in the immune system. They include natural killer cells (NK cells) (which function in cell-mediated, cytotoxic innate immunity), T cells (for cell-mediated, cytotoxic adaptive immunity), and B cells (for humoral, antibody-driven adaptive immunity).

macrophage cells

Immune cells that trap and engulf foreign cells and particles, scavenge cellular debris, and destroy infectious agents such as viruses, parasites, bacteria, and fungi.

magnetic resonance imaging (MRI)

A machine that produces images of the inside of the body using magnetic forces, without using x-rays.

malignant

Cancerous.

margin positive

When cancer cells are still present at the cutting edge (margin) of the removed prostate after surgery. A negative margin suggests that cancer cells are not present at the cutting edge as determined by a pathologist.

medical oncologist

A specialist in the treatment of cancer using chemotherapy.

metastasis/metastasise

The spread of cancer away from the place where it began.

metastatic prostate cancer

Cancer that has spread from the prostate to the pelvic bones and/or to other organs of the body.

micro-vesicles (cMV’s)

They are also called exosomes, circulating micro-vesicles, or micro-particles and are microscopic fragments of plasma membrane shed from almost all cell types. They have been implicated in the process of an anti-tumour reversal effect in cancer, tumour immune suppression, metastasis, and angiogenesis along with having a primary role in tissue regeneration.

Mi-Prostate Score (MIPS)

The MiPS test is an early detection test (pre-biopsy) for prostate cancer that combines the amount of serum PSA, with the amounts of two genes in the urine.

(DNA) mismatch repair (MMR)

A system for recognizing and repairing erroneous insertion, deletion, and mis-incorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage.

mitochondria

Mitochondria are organelles found in every cell within the body except in red blood cells. Mitochondria are unique because they contain their own copy of DNA. The mitochondria DNA generates 90% of a cell’s energy in the form of ATP (adenosine triphosphate). Perhaps more importantly, mitochondria have critical roles in regulating major metabolic pathways in the body.

molecular imaging biomarkers

Probes known as biomarkers are used in molecular imaging to help image particular targets or pathways.

monitoring

The process in which patients are subjected to follow up tests and/or clinical examination after the conclusion of initial diagnosis and treatment.

monotherapy

The treatment of cancer by using one form of therapy.

multiparametric MRI (mpMRI)

It is used to better identify and characterize prostate cancer. When T2-weighted, dynamic contrast enhanced, and diffusion-weighted imaging were used together the specificity and sensitivity for finding clinically significant prostate cancer (a Gleason score of 6 or higher and size exceeding 5 millimeters) was between 85 percent and 96 percent.

nadir

The lowest PSA reading reached after treatment for prostate cancer, before the PSA starts to rise again. This can occur some months after radiotherapy to cure prostate cancer.

neo-adjuvant therapy

Treatment given before another treatment to enhance its effectiveness.

neo-vascularity

The formation of a microvascular blood supply to feed a tumour.

nerve-sparing operation

Surgery for prostate cancer which aims to preserve the nerves which are essential for erections. The technique is not always possible as cancer can affect the areas around the nerves.

neutropenic fever

Also called febrile neutropenia. It is generally recognized as a complication of chemotherapy when it is myelosuppressive. (Suppresses the bone marrow from producing blood cells).

NK cells

A type of lymphocyte (a white blood cell) and a component of innate immune system. NK cells play a major role in the host-rejection of both tumours and virally-infected cells.

nomogram

Factors such as PSA, grade and stage are combined in a mathematical expression in order to predict outcomes such as the return of the cancer.

nucleotide

A compound consisting of a nucleoside linked to a phosphate group. Nucleotides form the basic structural unit of nucleic acids such as DNA.

oestrogens

They are the primary female sex hormones.

oncologist

A specialist in the treatment of cancer (see medical oncologist and radiation oncologist).

orchiectomy (sometimes called orchidectomy)

An operation that removes the testicles, but leaves the scrotal sac or scrotum.

osteomimicry

When cancer cells begin to express genes normally restricted to cells present within the bone. This change in gene expression allows cancer cells to avoid detection by the immune system and establish colonies in the bone micro-environment.

osteoporosis

Literally means ‘porous bones’. It occurs when bones lose a significant amount of their protein and mineral content, particularly calcium.

organelles

Organized or specialized structures within a living cell.

palliative care

Care of persons whose disease is not responsive to curative treatment. The goal of palliative care is achievement of the best possible quality of life for the person and their family.

pelvis

The area of the body located below the waist and surrounded by the hip and pubic bones.

pelvic floor muscles

These support the bladder and rectum and assist with stress incontinence by giving support to the bladder when coughing or sneezing.

pencil beam scanning

It is the movement of a charged particle beam such as a proton beam, where one or more properties of the beam such as intensity, size or position, are changed to ensure the delivery of the prescribed radiation dose.

penile plethysmograph

A medical device that measures the flow of blood in the penis.

penis

The male reproductive organ.

perineal (perineum)

The area of the body between the anus and the scrotum.

peripheral neuropathy

Damage to peripheral nerves that may impair sensation, movement, gland or organ function.

ph scale

The level of acidity or the alkalinity. Values below 7 are acidic and above 7 are alkaline.

phenotype

Its biochemical and physiological properties. An organism's phenotype results from two basic factors: the expression of an organism's genetic code, or its genotype, and the influence of environmental factors, which may interact, further affecting phenotype.

photodynamic therapy

It is a form of phototherapy using nontoxic light-sensitive compounds that are exposed selectively to light, whereupon they become toxic to targeted malignant and other diseased cells.

pituitary

The part of the brain that produces hormones which stimulate the testicles to produce testosterone.

positive emission tomography (PET)

A nuclear medicine functional imaging technique that is used to observe metabolic processes in the body as an aid to the diagnosis of disease. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radioligand, most commonly fluorine-18, which is introduced into the body on a biologically-active molecule called a radioactive tracer. 3D imaging is often accomplished with the aid of a computed tomography X-ray scan performed on the patient during the same session, in the same machine.

potency

The ability to have and maintain erections firm enough for penetration.

primary cancer

The original cancer. Cells from the primary cancer may migrate to other parts of the body, where secondary cancers might form.

protein kinases

A kinase enzyme that modifies other molecules, mostly proteins, by chemically adding phosphate groups to them (phosphorylation).

protein phosphorylation

A kinase is an enzyme that catalyses the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates. This process is known as phosphorylation, where the substrate gains a phosphate group and the high-energy ATP molecule donates a phosphate group.

prognosis

The likely development and outcome of a disease, as estimated by one's doctors.

prostatectomy

A surgical operation to remove all or part of the prostate.

prostate cancer

Localised: cancer confined within the prostate;

Locally advanced: contained within the prostate region and may include the seminal vesicles;

Advanced: cancer that has spread to adjacent organs such as the bladder, rectum and pelvic wall;

Metastatic: cancer that has spread to distant parts of the body.

prostate cancer risk calculator

A system that manually or on line, tallies responses to questions that determine the expected diagnosis type and stage of prostate cancer.

prostate gland

The gland that sits just below the bladder and opens into the urethra. It produces a fluid that forms part of semen. It is referred to in this book as the prostate.

prostate-specific antigen (PSA)

A protein produced by prostate cells, which is usually found in the blood in larger than normal amounts when prostate cancer is present. It is used as a test for prostate cancer or to monitor its recurrence.

prostatitis

Inflammation of the prostate brought about by an infection (or sometimes other causes).

proton beam therapy (PBT)

A type of conformal external beam radiotherapy which uses a beam of protons (instead of x-rays) to irradiate cancerous tissue. PBT reduces the radiation dose to normal tissue, with all parts of the cancer receiving the same radiation dose.

PSA bounce

A temporary rise in PSA reading experienced during the months after brachytherapy to cure prostate cancer. The cause is not well understood.

PSA density

A calculation that compares the PSA value with the size of the prostate which is measured by MRI or ultrasound.

PSA doubling time (PSADT)

The time it takes for the PSA result to double in value.

PSA velocity

How quickly the PSA level rises over time. It is a very important indicator as to the growth of the tumour.

quality of life

The appraisal of your situation and your well-being.

radiation

Energy in the form of waves or particles, including x-rays. This energy can injure or destroy cells by damaging their genetic material, which sees apostates (cell death) occur.

radiation oncologist

A specialist in the treatment of cancer using radiation techniques.

radical prostatectomy

An operation which removes the prostate, part of the urethra, a small part of both vas deferens and the seminal vesicles. This is usually done through a cut in the abdomen.

radical perineal prostatectomy (RPP)

A surgical procedure wherein the prostate gland is removed through an incision in the area between the anus and the scrotum (perineum).

radical retropubic prostatectomy (RRP)

A surgical procedure in which the prostate gland is removed through an incision in the abdomen.

radiotherapy

The use of radiation like x-rays or protons, to kill cancer cells.

RapidArc®

A new advanced non-surgical radiation therapy that destroys tumours using image-guided technology.

reactive oxygen species

A potent type of free radical which can deplete vitamin C levels and stimulates systemic inflammation.

rectum

The last part of the bowel, leading to the anus, through which faeces pass. The posterior of the prostate is immediately adjacent to the rectal wall.

recurrence

The re-occurrence of cancer some years after it was first treated.

remission

A term used to describe that there is no sign of cancer after treatment has concluded. It is not necessarily the same as 'cure', as any cancer cells present might not be discovered. In partial remission, some evidence of cancer still remains.

response

A change in the size or extent of the disease due to treatment.

reverse (or retrograde) ejaculation

This may occur after surgery for benign conditions of the prostate. The ejaculate travels back into the bladder instead of through the penis. This means a man is usually infertile, but an orgasm is still possible.

robot-assisted laparoscopic prostatectomy (RALP)

Minimally invasive surgery to remove the prostate. Small cuts are made in the abdomen. Surgery is conducted using telescopic instruments inserted through these cuts and controlled remotely by the surgeon with the aid of a computerised 'robot'.

salvage treatment

Further treatment to try to destroy cancer cells that survived the initial treatment and have since multiplied significantly. A form of radiation is usually used.

saw palmetto

As an extract, it is used by men with BPH. Clinical trials have not confirmed its efficacy, but it has a large following.

screening

Testing an at-risk population for a medical condition, to find people who have the condition, although obvious symptoms are not yet evident.

scrotum

A pouch of skin which hangs behind the penis and contains the testicles and some other parts of the male reproductive system.

secondary cancer

See metastasis.

semen

The fluid ejaculated from the penis at sexual climax.

seminal vesicles

Glands adjacent to the prostate that produce secretions which form part of the ejaculate.

shark cartilage

It is a dietary supplement made from the dried and powdered cartilage of a shark. It has been claimed that it provides therapeutic benefits when used for treating prostate cancer.

signalling pathways

In multi-cellular organisms, signal transduction pathways have evolved to regulate cell communication in a wide variety of ways. Each component (or node) of a signalling pathway is classified according to the role it plays with respect to the initial stimulus. Ligands are termed first messengers, while receptors are the signal transducers, which then activate primary effectors. Such effectors are often linked to second messengers, which can activate secondary effectors, and so on. Depending on the efficiency of the nodes, a signal can be amplified (a concept known as signal gain), so that one signalling molecule can generate a response involving hundreds to millions of molecules.

Most of these signalling pathways have significant importance in prostate cancer:

Akt/PKB signalling pathway

AMPK signalling pathway

cAMP-dependent pathway

Eph/ephrin signalling pathway

Hedgehog signalling pathway

Hippo signalling pathway

Insulin signal transduction pathway

JAK-STAT signalling pathway

MAPK/ERK signalling pathway

mTOR signalling pathway

Nodal signalling pathway

Notch signalling pathway

PI3K/AKT/mTOR signalling pathway

TGF beta signalling pathway

TLR signalling pathway

VEGF signalling pathway

Wnt signalling pathway

SIR-spheres

Resin based microspheres with an average diameter between 20 and 60 micrometres. The microspheres are impregnated with ^{90}Y, a beta radiating isotope of yttrium with a half-life of 64.1 hours.

stage/staging

A system for describing how far the cancer has spread. The most common is the TNM system with T standing for the tumour size; N for lymph nodes and M for metastasis.

stem cells

There are 5 types of stem cells. Of most relevance are unipotent stem cells which produce only one cell type, their own; but have the property of self-renewal, which distinguishes them from non-stem cells `like progenitor cells, which cannot self-renew.

stereotactic beam radiation therapy (SBRT)

SBRT involves the delivery of a single high dose radiation treatment or a few fractionated radiation treatments (usually up to 5 treatments). The radiation is delivered using a specially designed coordinate-system that precisely monitors the location of fiducial markers implanted in the tumour before the radiation begins. This specialized form of radiation involves the use of multiple radiation beam angles to maximise the radiation dose to the tumour whilst minimising radiation to adjacent healthy tissue.

stress incontinence

Uncontrolled loss of a small amount of urine as a result of laughing, coughing, sneezing or any strenuous activity, such as lifting heavy objects.

stricture

When urine flow is obstructed by a narrowing of the urethra by injury or disease.

surgery

An operation or a medical procedure involving an incision or cut in order to investigate or treat a medical condition.

surgical margin

After a radical prostatectomy, the edges of the tissue that has been removed are visually examined to see if cancer cells are present. If they are not (negative surgical margins) the chance is higher that all of the cancer has been removed. A pathologist often reviews the removed tissue to check the surgical margin for remaining cancer.

survival

Prostate cancer specific: the proportion of men who survive for a given period, say five years.

Biochemical: the proportion of men surviving without an increase in PSA levels for a given period, say five years.

testicles

Organs in the scrotum which produce sperm and the male hormone, testosterone.

testosterone

The major male hormone which is mainly produced by the testicles.

testosterone flare

The surge in testosterone levels that is seen when treating patients with GnRH agonists.

tissue

A collection of cells.

TNM system

The TNM Classification of Malignant Tumours is a cancer staging system that describes the extent of a person's cancer.

T describes the size of the original (primary) tumour and whether it has invaded nearby tissue.

N describes nearby (regional) lymph nodes that are involved.

M describes distant metastasis (spread of cancer from one part of the body to another).

tomo therapy

A type of radiation therapy in which the radiation is delivered slice-by-slice. This method of delivery differs from other forms of external beam radiation therapy in which the entire tumour volume is irradiated at one time.

transcription

The first step of DNA based gene expression, in which a particular segment of DNA is copied into RNA (especially mRNA) by the enzyme RNA polymerase. Both DNA and RNA are nucleic acids, which use base pairs of nucleotides as a complementary language. During transcription, a DNA sequence is read by an RNA polymerase, which produces a complementary, anti-parallel RNA strand called a primary transcript.

transcriptomes

The specific sub-set of transcripts (instructions) present in a particular cell type.

translation

The process in which ribosomes in the cytoplasm or ER synthesize proteins after the process of replication of DNA to RNA in the cell's nucleus. The entire process is called gene expression.

transrectal ultrasound (TRUS)

Used for the evaluation of the prostate in men with elevated PSA or prostatic nodules on DRE. It may reveal prostate cancer, BPH, or prostatitis and its imaging capability is also used to help guide a prostate biopsy needle. The ultrasound probe is inserted in the rectum.

transurethral resection of the prostate (TURP)

An operation for BPH of the prostate, but sometimes used to treat prostate cancer. An instrument is inserted, under anaesthetic, along the urethra and removes prostate tissue which may be blocking the flow of urine.

tumour

Any abnormal growth of tissue which may be benign or cancerous.

tumour mutational burden

The number of mutations within a targeted genetic region in the cancerous zone.

urethra

The tube which carries urine and ejaculate along the length of the penis and then to exit the body.

uroflowmetry

Free uroflowmetry test: measures how fast the patient can empty his bladder.

Pressure uroflowmetry test: measures the rate of voiding, and simultaneous assessment of bladder and rectal pressures.

urologist

A medical specialist who diagnoses and treats urological conditions.

vas deferens

Ducts that take sperm to the urethra on ejaculation.

virotherapy

A treatment using biotechnology to convert viruses into therapeutic agents by reprogramming viruses to treat diseases.

watchful waiting

An approach to low grade prostate cancer where medical intervention or therapy is delayed until repeat testing may suggest the need for intervention.

whole body hyperthermia

A medical treatment in which the body is exposed to elevated temperatures that kill cancer cells, whilst doing no damage to healthy cells.

x-ray

A form of electromagnetic radiation.

ZIP1-deficieny

The protein ZIP1 is responsible for the active transport of zinc into prostate cells. This transport mechanism is often compromised in prostate cancer.

Appendix 2.

Abbreviations

3D-CRT	conformal radiotherapy
ADT	androgen deprivation therapy
ASI	androgen synthesis inhibitors
ASTRO	American Soc. for Therapeutic Radiology and Oncology
ATP	adenosine triphosphate
AUA	American Urological Association
BPH	benign prostate hypertrophy
CIPC	clinically insignificant prostate cancer
CNS	central nervous system
CRCP	metastatic castration-resistant prostate cancer
CT	computerised tomography
DCE-MRI	dynamic contrast enhanced MRI
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
DRE	digital rectal examination
DW-MRI	diffusion-weighted MRI
EBRT	external beam radiation therapy
EPIC	Expanded Prostate Cancer Index Composite
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FDA	US Food and Drug Administration
FLA	focal laser ablation
Gy	gray
HCL	Harvard Cyclotron Laboratory
HDR	HDR brachytherapy
HIFU	high intensity focused ultrasound
IGRT	image-guided radiotherapy
IIEF-15	The International Index of Erectile Function-15
IMPT	intensity modulated proton therapy
IMRT	intensity modulated radiotherapy
IPSS	The International Prostate Symptom Score
KMI	Korean Medical International
LDR	LDR brachytherapy

Abbreviations (Continued)

LLUMC	Loma Linda University Medical Centre
MHz	megahertz
MiPS	Mi-Prostate Score
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
NCC	National Cancer Centre, South Korea
NCCN	US National Comprehensive Cancer Network
NHA	new generation hormonal agents
PBT	proton beam therapy
PET	positron emission tomography
PI-RADS	Prostate Imaging Reporting and Data System
PSADT	PSA doubling time
RALP	robot-assisted laparoscopic prostatectomy
RCT	randomised clinical trials
RF	radio frequency
RDA	recommended daily allowance
RNA	ribonucleic acid
RPP	radical perineal prostatectomy
RRP	radical retropubic prostatectomy
SBRT	stereotactic beam radiation therapy
TCM	traditional Chinese medicine
TGA	Therapeutic Goods Administration (Australia)
TRUS	transrectal ultrasound
TUH	transurethral hyperthermia
TURP	transurethral resection of the prostate
UCL	University College of London
UCLA	University of California of Los Angeles
UCLH	University College of London Hospital
USPSTF	US Preventative Services Task Force
WBH	whole body hyperthermia

Appendix 3.

Resource Listing

Chapter 2. What is Prostate Cancer?

The Rezum system.

http://www.rezum.com

Chapter 3. How is Prostate Cancer detected?

The USPSTF full report.
https://www.uspreventiveservicestaskforce.org/Page/Document/Recommenda
cancer-screening1

The USPSTF one-page summary report.

https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummary
cancer-screening1?ds=1&s=prostate

The AUA new PSA testing guidelines.

https://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm

Interesting Questions and Answers on MiPS.

http://www.mlabs.umich.edu/files/pdfs/MiPS_FAQ.pdf

More information on mpMRI and prostate cancer.

http://www.cancernetwork.com/prostate-cancer/state-prostate-mri-2013/page/0/1#sthash.5i1qxGq6.dpuf.

UCLA combines the use of an MRI with advanced Doppler ultrasound technology to produce a 3D 'fusion' image.

See video. http://urology.ucla.edu/body.cfm?id=455.

Details of the Tissue Harmonic technology with Colour Doppler TRUS practiced by Dr. Duke Bahn, Prostate Institute of America.

http://pioa.org/about-prostate-cancer/accurate-staging/color-doppler-tissue-harmonic-ultrasound/

PCPTR2.0 Calculator

http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp

Sunnybrook Prostate Cancer Risk Calculator

http://sunnybrook.ca/content/?page=occ-prostateriskca.

The SWOP Prostate Cancer Research Foundation in association with the European Randomized Study of Screening for Prostate Cancer.

http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators.

The Memorial Sloan Kettering Cancer Centre Prostate Cancer Nomograms.

https://www.mskcc.org/nomograms/prostate

Chapter 4. Imaging

68Ga-PSMA PET/CT vs. mpMRI for loco-regional prostate cancer staging:

correlation with final histopathology.

http://www.ncbi.nlm.nih.gov/pubmed/29858591

Chapter 6. Watchful Waiting or Active Surveillance

The US National Comprehensive Cancer Network has recently updated their Prostate Cancer Guidelines.

http://www.nccn.org/patients/guidelines/prostate/index.html#1.

PSA doubling time (PSADT) is a very important parameter in judging the degree of aggressiveness of the cancer.

http://prostate-cancer.org/active-surveillance-for-favorable-risk-prostate-cancer-what-are-the-results-and-how-safe-is-it/

Chapter 7. Surgery

da Vinci® Surgery Web Site

http://www.davincisurgery.com/da-vinci-urology/conditions/prostate-cancer/da-vinci-prostatectomy/

The da Vinci ®Surgery web site compares patient outcomes for open, laparoscopic and da Vinci® RALP surgery.

http://www.davincisurgery.com/da-vinci-urology/treatment-comparison/da-vinci-vs-open-lap.php

What are pelvic floor muscles?

http://www.continence.org.au/pages/pelvic-floor-men.html

WebMD Web Site

http://www.webmd.com/urinary-incontinence-oab/kegel-exercises-treating-male-urinary-incontinence

Chapter 8.1 External Beam Radiation Therapy

SpaceOAR® System – Spacing Organs At Risk.

http://www.augmenix.com/products/spaceoar/

Chapter 8.4 Proton Beam Therapy

A paper: “Proton beam therapy and localized prostate cancer: current status and controversies.”

http://www.nature.com/bjc/journal/v108/n6/full/bjc2013100a.html.

Chapter 8.5 Low Dose Rate Brachytherapy (Seeds)

An excellent web site on LDR brachytherapy.

http://www.cancerresearchuk.org/cancer-help/type/prostate-cancer/treatment/radiotherapy/internal-radiotherapy-for-prostate-cancer#quick

Chapter 8.7 Radioactive Ligand Therapy

Germany teaching hospitals offering RLT.

https://bookinghealth.com/programs/treatment/nuclear-medicine/prostate-cancer-with-metastasis-lutetium-177-psma

Theranostics Australia, Perth, Western Australia.

http://theranostics.com.au/

Chapter 9. Hyperthermia

Further details on non-local hyperthermia.

http://en.wikipedia.org/wiki/Hyperthermia_therapy#Mechanism.

Chapter 10. Cryosurgery

Best Practice Policy Statement on Cryosurgery for the Treatment of Localized Prostate Cancer.

http://www.auanet.org/education/guidelines/cryosurgery.cfm.

Chapter 13. Hormone Therapy

The Galeterone (ARMOR3-SV) clinical trial.

http://www.pcf.org/site/c.leJRIROrEpH/b.5849073/k.9B21/Clinical_Trials.htm

The NCCN Clinical Practice Guidelines in Oncology

(NCCN Guidelines®)

https://www.nccn.org/professionals/physician_gls/default.aspx

The AUA Guidelines for Castrate-Resistant Prostate Cancer

https://www.auanet.org/guidelines/prostate-cancer-castration-resistant-guideline

Chapter 14. Chemotherapy and Immunotherapy

The AUA Guidelines for Castrate-Resistant Prostate Cancer

https://www.auanet.org/guidelines/prostate-cancer-castration-resistant-guideline

An excellent pictorial illustration of the path to successful immunotherapy discovery and treatment.

http://www.cancerresearch.org/cancer-immunotherapy/what-is-cancer-immunotherapy.

When prostate cancer continues to grow treatment, options become more limited.

http://www.cancerresearch.org/prostate-cancer #sthash.IP5NLb41.dpuf.

A Study of Sipuleucel-T with Administration of Enzalutamide in Men with Metastatic Castrate-Resistant Prostate Cancer.

https://clinicaltrials.gov/ct2/show/NCT01981122

Cancer Vaccine Developments.

http://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet#q4

The Oncotype DX AR-V7 Nucleus Detect test.

https://www.genomichealth.com/en-US/Advocacy/ARV7_Nucleus_Detect_Test

Chapter 15. Metastatic Prostate Cancer, Diagnosis, Genetics and Precision Medicine

Caris Life Sciences profiling service.

http://www.carislifesciences.com

Chapter 17. Sexual Function and Incontinence

Dovetail Erectile Dysfunction App

https://www.narrative.org/post/can-an-app-help-treat-ed

Chapter 18. The Plan to Successfully Fight Off Cancer

Biomagnetic Therapy

https://innovativemedicine.com/biomagnetic-therapy/

Hidden Dangers in Personal Care Products Infographic.

http://www.mercola.com/infographics/personal-care-products.htm

10 Dangerous Everyday Things in Your Home.

http://articles.mercola.com/sites/articles/archive/2008/12/23/10-dangerous-everyday-things-in-your-home.aspx

Chapter 19. Complementary Therapies

Dr Charles ‘Snuffy’ Myers Prostatepedia web site.

http://www.prostatepedia.net/pages/dr-myers

Ron Gellatley’s books.

http://www.health-e-books.com/index.html

Chapter 20. Diet and Nutrition

The 5 Most Dangerous Lies You've been told about Bread.

http://betterbreads.net/

Curcuma 100: A water soluble supplement with the highest availability of curcumin.

https://www.lifeintegrativemed.com/en/health-products/70-curcuma-100.html

Essiac Tea Mixture.

http://essiacfacts.com/essiac-tea-benefits-for-health/

The American Cancer Society – A list of Herbs, Vitamins and Minerals under the Complementary and Alternative Medicine category.

http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalte

Selenium and Vitamin E Cancer Prevention (SELECT) trial.

http://www.ncbi.nlm.nih.gov/pubmed/21990298

"The New Prostate Cancer Nutrition Book." Dr Charles 'Snuffy' Myers.

http://www.prostatepedia.net/collections/book

CANCERactive Web Site.

http://www.canceractive.com

The US National Cancer Institute’s comments on pomegranate juice.

http://www.cancer.gov/cancertopics/pdq/cam/prostatesupplements/healthprofessi

Chapter 21. Alternative Therapies

The Truth about Cancer.

https://thetruthaboutcancer.com/author/janegoldberg/

Liposomal Vitamin C.

http://www.peakenergy.com/articles/nh20140311/Reversing-disease-with-the-'multi-C'-protocol

A Tide of Evidence washes away Flawed Fish Oil PCa Study.

http://anhinternational.org/2013/07/17/a-tide-of-evidence-washes-away-flawed-fish-oil-prostate-cancer-study/

"The Complete Guide to Alternative Cancer Treatments."

http://www.cancerdefeated.com/publications/

Ty Bollinger's "The Truth about Cancer – A Global Quest."
http://www.icr.ac.uk/press/recent_features_articles/Story_Abiraterone/index

"How to Cure Almost Any Cancer at Home for $5.15 a Day."

http://www.curecancerathome.com/515/index.php?SC=CDHOME

Chapter 23. The Role of Support Groups

The "Informed Prostate Cancer Support Group" (IPCSG).

http://www.ipcsg.org/

Us Too International

http://www.ustoo.org

Chapter 30. How Do You Get to a Final Treatment Decision?

Dr John McHugh's Decision Worksheet/Cheat Sheet.

http://theprostatedecision.wordpress.com/mchugh-decision-worksheetcheatsheet/

Appendix 4.

Reference Listings

Chapter 1. I am Diagnosed with Prostate Cancer

1. Bratt O, et al., Hereditary Prostate Cancer: Clinical Aspects. The Journal of Urology, Vol. 168, 906–913, September 2002.

Chapter 2. What is Prostate Cancer?

1. Australian Institute of Health and Welfare. Incidence and Prevalence of Chronic Disease, 2009. http://www.aihw.gov.au/cdarf/data_pages/incidence_prevalence/index.cfm#Diabe

Chapter 3. How is Prostate Cancer Detected?

1. Thompson IM, et al., Prevalence of prostate cancer among men with a PSA level < or =4.0 ng per millilitre. New England Journal of Medicine, 2004; 350(22): 2239-46.

2. Boots WebMD Web site. Prostate Cancer Guide. http://www.webmd.boots.com/prostatecancer/guide/psa-test-prostate-cancer.

3. See 1 and 2 above.

4. El Camino Urology Medical Group web site. Prostate Cancer. http://www.elcaminourology.com/PSAandProstateCancer.html.

5. Scosyrev, E, et al., PSA screening for prostate cancer and the risk of overt metastatic disease at presentation: Analysis of trends over time. Cancer. 2012 Dec 1; 118 (23):5768-76.

6. Hunter Prostate Cancer Alliance web site. http://www.hpca.org.au/pcfmenu/testingmenu/item/51-morepsa.html#Density

7. Prostate Health Index (phi). FDA Approves New Blood Test to Improve Prostate Cancer Detection, June 2012.

8. Clinical Information about the 4K score Test. OPKO Diagnostics. http://clinical.opko.com/how-does-4kscore-test-work.

9. Pre-treatment Genetic Test Predicts Recurrence in Prostate Cancer. http://www.onclive.com/web-exclusives/Pretreatment-Genetic-Test-Predicts-Recurrence-in-Prostate-Cancer#sthash.jlEIkaKK.dpuf.

10. Castro E, Goh C, Saunders E, et al., Germline BRCA Mutations Are Associated With Higher Risk of Nodal Involvement, Distant Metastasis, and Poor Survival Outcomes in Prostate Cancer. JCO May 10, 2013 vol. 31 no. 14

1748-1757.

11. Pokorny MR, de Rooij M, et al., Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound–Guided Biopsy Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies. Eur Urol. 2014 Jul; 66(1):22-9.

12. Bonekamp D, Jacobs MA, El-Khouli R, et al., Advancements in MR imaging of the prostate: from diagnosis to interventions. Radiographics 31 (3 Suppl): 677–703. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3093638/.

13. Rothwax JT, George AK, et al., Multiparametric MRI in Biopsy Guidance for Prostate Cancer: Fusion-Guided. BioMed Research International, Volume 2014, Article ID 439171.

14. Bloch BN, Genega EM, Costa DN, et al., Prediction of prostate cancer extracapsular extension with high spatial resolution dynamic contrast-enhanced 3-T MRI. Eur Radiol. 2012 Oct; 22(10): 2201-10.

15. Barentsz JO, Richenberg J, Clements R, et al., ESUR prostate MR guidelines 2012. European Radiology 2012 10.1007/s00330-011-2377-y.

16. Junker D, Schäfer G, Edlinger M, et al., Evaluation of the PI-RADS Scoring System for Classifying mpMRI Findings in Men with Suspicion of Prostate Cancer. BioMed Research Int. Vol. 2013 (2013), Article ID 252939.

17. McKiernan J, Donovan M, O’Neill V, et al., A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. JAMA Oncol. March 31, 2016. doi:10.1001/jamaoncol.2016.0097.

18. Kasivisvanathan, V., et al., Prostate evaluation for clinically important disease: Sampling using image-guidance or not? (The PRECISION study). European Urology Supplements, Volume 17, Issue 2, e1716 - e1717.

Chapter 5. Introductory Comments on Treatment Options

1. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. Lancet 2003 l.: 361: 1243-52.

2. Barocas DA, et al., Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. JAMA. 2017;317(11):1126-1140. doi:10.1001/jama.2017.1704.

Chapter 6. Active Surveillance

1. Ip S, Dahabreh IJ, Chung M, et al., An evidence review of active surveillance in men with localized prostate cancer. Evid Rep Technol Assess (Full Rep). 2011 Dec; (204):1-341.

2. Mohler JL. Roswell Park Cancer Institute and chair of the NCCN Guidelines Panel for Prostate Cancer, Presentation at the NCCN 16th Annual Conference in the USA.

3. Klotz L, Zhang L, Lam A., et al. Clinical results of long-term follow-up of a large active surveillance cohort with localised prostate cancer. J Clin Oncol 2010; 28: 126–31.

4. Sung Kyu Hong. Clinically insignificant prostate cancers: are they really insignificant?
http://approstate.org/workshop/201101/program/files/APPS_Sung%20Kyu%20H

5. Wolters T, Roobol MJ, van Leeuwen PJ, et al., A critical analysis of the tumour volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. J Urol. 2011 Jan; 185(1): 121-5.

6. Jeldres C, Suardi N, Walz J, et al., Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. Eur Urol. 2008 Dec; 54(6): 1306-13. Epub 2007 Dec 7.

7. Mottet N, Bastian PJ, Bellmunt J, et al., Pocket Guidelines on Prostate Cancer Updated April 2014. European Urology Association.

8. See 5 above.

Chapter 7. Surgery

1. Rozet F, et al., Dept of Urology, Institut Montsouris, Paris, France. A Direct Comparison of Robotic Assisted Versus Pure Laparoscopic Prostatectomy: A

Single Institution’s Experience.
http://www.abmedica.it/Rozet%20J%20Urol%202007.pdf

2. Lepor H. Smilow Comprehensive Prostate Cancer Centre Web Site
http://prostatecancer.med.nyu.edu/treatment/prostate-cancer-surgery

3. Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate. 1983; 4(5): 473-85.

4. Marien T, Sankin A, Lepor H. Factors predicting preservation of erectile function in men undergoing open radical retropubic prostatectomy. J Urol. 2009 Apr; 181(4): 1817-22.

5. Jacobs EFP, Boris R, et al., Advances in Robotic-Assisted Radical Prostatectomy over Time. Prostate Cancer, Vol. 2013 (2013), Article ID 902686.

6. Ahlering T. Department of Urology, University of California, Irvine.
http://www.urology.uci.edu/prostate/index.html.

7. Australian Institute of Health and Welfare. Incidence and Prevalence of Chronic Disease, 2009.
http://www.aihw.gov.au/cdarf/data_pages/incidence_prevalence/index.cfm#Diab

8. Park JJ, Kim CK, Park SY, et al., Prostate Cancer: Role of Pre-treatment Multiparametric 3-T MRI in Predicting Biochemical Recurrence After Radical

Prostatectomy. AJR Am J Roentgenol. 2014; 202:W459-W465.

Chapter 8. Radiation

1. Frank SJ, Pisters LL, Davis J, et al., An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol. 2007 Jun; 177(6): 2151-6; discussion 2156.

2. Prostate Cancer Foundation of Australia. External Beam Radiotherapy. http://www.prostate.org.au/articleLive/pages/External-BeamRadiotherapy.html

3. Feng FY, Blas K, Olson K, et al., Retrospective evaluation reveals that long-term androgen deprivation therapy improves cause-specific and overall survival in the setting of dose-escalated radiation for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2013 May 1; 86(1): 64-71.

4. Erectile Dysfunction Guidance web site: EBRT and Viagra. http://edguidance.com/viagra/.

5. Kosuri S, Aktar NH, Smith M, et al., Review of Salvage Therapy for Biochemically Recurrent Prostate Cancer: The Role of Imaging and Rationale for Systemic Salvage Targeted Anti-Prostate-Specific Membrane Antigen Radio-immunotherapy. Advances in Urology, Vol. 2012 (2012), Art ID 921674.

6. Pound CR, Partin AW, Eisenberger MA, et al., Natural History of Progression

after PSA Elevation Following Radical Prostatectomy. JAMA 1999; 281:1591–7. PMID: 10235151.

7. Roehl KA, Han M, Ramos CG, et al., Cancer Progression and Survival Rates Following Anatomical Radical Retropubic Prostatectomy in 3,478 Consecutive Patients: Long-Term Results. J Urol. 2004; 172:910–14. PMID: 15310996.

8. See 5 above.

9. Garnick MB. How to handle a relapse after treatment for prostate cancer. Prostate Knowledge, Harvard Medical School. http://www.harvardprostateknowledge.org/ how-to-handle-a-relapse-after-treatment-for-prostate-cancer.

10. Mangar SA, Huddart RA, Parker CC, et al., Technological advances in radiotherapy for the treatment of localised prostate cancer. Eur J Cancer. 2005 Apr; 41(6): 908-21.

11. IMRT for prostate cancer. Cancer Centers of America web site. http://www.cancercenter.com/prostate-cancer/imrt/.

12. Kirichenko, A, et al., IMRT versus 3D CRT for prostate cancer, new long-term data assesses side effects. http://psychcentral.com/news/archives/2006-11/fccc-iv3110106.html.

13. Sharma, NK, Li, T., Chen, DY., et al., IMRT Reduces Gastrointestinal

Toxicity in Patients treated with ADT for Prostate Cancer. Int J Rad Onco•Biology•Physics 2011; 80 (2): 437-444.

14. Zhou GX, Xu SP, Dai XK, et al., Clinical dosimetric study of three radiotherapy techniques for postoperative breast cancer: Helical Tomotherapy, IMRT, and 3D-CRT. Technol Cancer Res Treat. 2011 Feb; 10(1):15-23.

15. RapidArc® - the next dimension in speed and precision. http://www.varian.com/euen/oncology/treatments/treatment_techniques/rapidarc/

16. Stereotactic Body Radiotherapy for Primary Management of Early-Stage, Low- to Intermediate-Risk Prostate Cancer: Report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. http://www.redjournal.org/article/S0360-3016(09)03543-3/fulltext

17. UCLA Health. Radiation Oncology UCLA. Stereotactic Body Radiotherapy for Prostate Cancer. http://radonc.ucla.edu/body.cfm?id=244.

18. King CR, James D. Brooks JD, et al., Long-Term Outcomes from a Prospective Trial of Stereotactic Body Radiotherapy for Low-risk Prostate Cancer. http://radonc.ucla.edu/workfiles/SBRT/Prostate_SBRT_Patient_Info.pdf

19. Yu JB, Cramer LD, Herrin J, et al., SBRT Vs IMRT for Prostate Cancer: Comparison of Toxicity. JCO March 10, 2014 JCO.2013.53.8652.

20. West Australian Dept. of Health. Sir Gairdner Hospital, Perth, West

Australia, Australia. CyberKnife Robotic Radiosurgery System Patient Information Sheet.
http://www.scgh.health.wa.gov.au/OurServices/CancerCentre/RadiationOncology

21. Zietman AL, DeSilvio ML, Slater JD, et al., Comparisons of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. J. A. M. A. 294 (10, 1233-1239 (2005).

22. Foote RL, Stafford SL, Petersen IA, et al., The clinical case for proton beam therapy. Radiation Oncology 2012, 7:174

23. Efstathiou JA. A Landmark Study Compares Proton Beam Therapy with Standard Radiation Therapy. Advances at Mass. General Cancer Center - Fall 2013.
http://www.massgeneral.org/cancer/assets/advancesincancer/ADVQ413_Cancer_
(2).pdf.

24. Talcott A, Rossi C, Shipley WU, et al., Patient-Reported Long-term Outcomes After Conventional and High-Dose Combined Proton and Photon Radiation for Early Prostate Cancer. JAMA. 2010; 303(11): 1046-1053.

25. As 21 above.

26. Chung CS, Keating N, Yock T, Tarbell N. Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy. Int J Radiat Oncol Biol Phys. Vol. 72, Supp, PS8, Sept 2008.

27. Fontenot JD, Lee AK, Newhauser WD. Risk of secondary malignant neoplasms from proton therapy and intensity-modulated x-ray therapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys. 2009 Jun 1; 74(2): 616-22.

28. Allen AM, Pawlicki T, Dong L. An evidence-based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiother Oncol. 2012 Apr; 103(1): 8-11.

29. Efstathiou, JA, Gray PJ, Zietman AL. Proton Beam Therapy and Localised Prostate Cancer: Current Status and Controversies. British Journal of Cancer 108, no. 6 (April 2, 2013): 1225–1230.

30. Lawenda BD. Proton Beam Therapy: The Rolls Royce of Radiation Oncology. http://www.integrativeoncology-essentials.com/2013/03/proton-beam-therapy-the-rolls-royce-of-radiation-oncology/#sthash.6sONAuAD.aq4qTINH.dpuf.

31. Grimm P, Billiet I, Bostwick D, et al., Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high-risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int. 2012 Feb; 109 Suppl 1:22-9.

32. Langley SEM, Laing RW. 4D Brachytherapy - a novel real-time prostate brachytherapy technique using stranded and loose seeds. BJU Int. Vol. 109, Issue Supp s1, pages 1–6, Feb 2012. http://www.4dbrachytherapy.com/index.php/overview.

33. Hsu I-Chow, Yamada Y, Vigneault E, Pouliot J. Generalized Criteria for the use of Brachytherapy in the treatment of Prostate Cancer August 2008. American Brachytherapy Society Prostate High-Dose Rate Task Group. http://www.americanbrachytherapy.org/guidelines/HDRTaskGroup.pdf.

34. Hofman MS, et al., [177Lu]-PSMA-617 radionuclide treatment in patients with mCRPC. Lancet Oncology 2018 Jun, 19(6):825-833.

35. Kratochwil C, et al., Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer with 225Ac-PSMA-617. J Nucl Med 2018; 59:795-802.

36. Efstathiou, Jason A., External Beam Radiation Therapy for High-Risk/Locally Advanced Prostate Cancer: The Shifting Landscape. April 12, 2019. Accessed Aug 2019. https://grandroundsinurology.com/external-beam-radiation-therapy-for-high-risk-locally-advanced-prostate-cancer-the-shifting-landscape/

37. Fiorillo, M., Doxycycline, Azithromycin and Vitamin C: A potent combination therapy for targeting mitochondria and eradicating cancer stem cells. Aging (Albany NY). 2019 Apr 19;11(8):2202-2216.

38. Jackson, WC., et al., Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. Int. J. Radiat. Oncol. Biol. Phys 2019 Jul 15;104(4)778-789.

Chapter 9. Hyperthermia

1. Lieberman S. A Review of Whole Body Hyperthermia and the Experience of Klinik St.Georg, Townsend Letter, Aug/Sept 2009, http://kstg.net/e/publications/pdf/a_review_of_whole_body_hyperthermia_and_t
st-georg.html.

2. van der Zee J., Heating the patient: a promising approach? Ann Oncol. 2002 Aug; 13(8):1173-84.

3. Douwes FR, Lieberman S., Radio-frequency Transurethral Hyperthermia and Complete Androgen Blockade. Jnl of Alternative & Complementary Therapies 7:6: 291-295, 2001.

4. Oleson RO, Samulski TV, Leopold KA, et al., Sensitivity of hyperthermia trial outcomes to temperature and time: Implications for thermal goals of treatment. Int Jour of Rad Onco.Biol.Physics Vol. 25, Issue 2, 15 Jan 1993.

5. The Science of Hyperthermia, Albathermia Web Site, http://www.albahyperthermia.com/hyperthermia-overview.html.

6. Falk MH, Issels RD., Hyperthermia in oncology. Int J Hyperthermia. 2001 Jan-Feb; 17(1):1-18.

Chapter 10. Cryosurgery

1. Babaian RJ, Donnelly B, Bahn D, et al. (Panel Members). Best Practice Policy

Statement on Cryosurgery for the Treatment of Localized Prostate Cancer. American Urological Association. http://www.auanet.org/education/guidelines/cryosurgery.cfm.

2. Heidenreich A, Locally Recurrent Prostate Cancer Following Radiation Therapy: To Cut or To Freeze? European Urology, Volume 64 Issue 1, July 2013, Pages 8-10.

3. Bahn DK, Lee F, Badalament R, et al., Targeted Cryoablation of the Prostate: 7-Year Outcomes in the Primary Treatment of Prostate Cancer. Urology Vol 60, (Suppl 2A): 3–11, 2002.

4. Ex - Director of the Prostate Cancer Institute, St. George Hospital, Sydney, Australia. Comments on the Institute's web site. http://www.prostatecancer.org.au/PCI/News.html.

5. Onik G, Vaughan D, Lotenfoe R, et al., 'Male lumpectomy': focal therapy for prostate cancer using cryoablation. Urology. 2007 Dec; 70(6 Suppl): 16-21.

Chapter 11. High Intensity Focussed Ultrasound

1. Roundy N. HIFU Treatment Data is Maturing. PCRI Insights, March 2011, Vol. 14: No 1. http://prostate-cancer.org/PDFs/Is14-1_p14-20.pdf.

2. Brosman S. HIFU – Not Ready For Prime Time. PCRI Insights, March 2011, Vol. 14: No 1.

3. Lukka H, Waldron T, Chin J, et al., High-intensity focused ultrasound for prostate cancer: a systematic review. Clin Oncol (R Coll Radiol). 2011 Mar; 23(2): 117-27.

4. Ahmed HU, Freeman A, Kirkham A. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011 Apr; 185(4): 1246-54.

5. Hindley RG, Dickinson L, Freeman A. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. The Lancet Oncology, Vol. 13, Issue 6, Pg 622 - 632, June 2012.

6. Cordeiro ER, Cathelineau X, Thüroff S, et al., High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer. BJU Int. 2012 Nov; 110(9): 1228-42.

7. Obyn C, Mambourg F. Assessment of high intensity focused ultrasound for the treatment of prostate cancer. Acta Chir Belg. 2009 Oct; 109(5): 581-6.

8. Dickinson L, Hu Y, Ahmed HU, et al. Image-Directed, Tissue-Preserving Focal Therapy of Prostate Cancer: A Feasibility Study of a Novel Deformable MR-US Registration System. BJU Int. Vol. 112, Issue 5, pages 594–601, Sept 2013.

9. Scionti S. Targeted Focal Prostate Cancer Treatment. Scionti Prostate Centre Web Site: http://www.drscionti.com/targeted-focal-prostate-cancer-treatment.

Chapter 12. Focal Laser Ablation

1. Smilow Comprehensive Prostate Cancer Centre, NYULMC: http://prostate-cancer.med.nyu.edu/treatment/focal-laser-ablation-prostate-cancer.

2. Turkbey B, Ravizzini G, Mani H, et al.,3T MR Imaging of the Prostate Gland: What the Urologist Needs to Know. National Cancer Institute, NIH, USA. http://www.baristurkbey.com/images/prostate poster.pdf.

3. Costa DN, Bloch BN, Yao DF, et al., Diagnosis of relevant prostate cancer using supplementary cores from magnetic resonance imaging-prompted areas following multiple failed biopsies. Magnetic Resonance Imaging Jul 2013, 31(6); 947-952.

4. Sperling D, Sperling Prostate Centre http://sperlingprostatecenter.com/

5. Oto A, Sethi I, Karczmar G, et al., MR imaging-guided focal laser ablation for prostate cancer: phase I trial. Radiology. 2013 Jun; 267(3): 932-40.

6. Smilow Comprehensive Prostate Cancer Centre, NYULMC: http://prostate-cancer.med.nyu.edu/treatment/focal-laser-ablation-prostate-cancer.

7. Mottet N, Bastian PJ, Bellmunt J, et al., Guidelines on Prostate Cancer Updated April 2014. European Urology Association. http://www.uroweb.org/gls/pdf/1607%20Prostate%20Cancer_LRV3.pdf.

8. Mottet N, Bastian PJ, Bellmunt J, et al., Pocket Guidelines on Prostate Cancer Updated April 2014. European Urology Association. http://www.uroweb.org/gls/pockets/english/PCProstate%20Cancer_LR.pdf

Chapter 13. Hormone Therapy

1. Xtandi Phase 111 Clinical Trial Web Site. https://www.xtandihcp.com/phase-3-trial-design.

2. Higano CS, et al., Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer. https://doi.org/10.1002/cncr.32445.

3. Abiraterone: a story of scientific innovation and commercial partnership. Institute of Cancer Research, UK. http://www.icr.ac.uk/press/recent_features_articles/Story_Abiraterone/index.shtm

Chapter 14. Chemotherapy and Immunotherapy

1. Metastatic Cancer. National Cancer Institute Fact Sheet. http://www.cancer.gov/cancertopics/factsheet/Sites-Types/metastatic.

2. What biophosphonates are. Cancer Research UK. http://www.cancerresearchuk.org/cancer-help/about-cancer/treatment/bisphosphonate/what-bisphosphonates-are.

3. Sartor O, Eisenberger M, Kattan MW, et al., Unmet Needs in the Prediction and Detection of Metastates in Prostate Cancer. The Oncologist Express, May 6, 2013.

4. Sweeney C, Chen Y, Carducci MA, et al., Impact on overall survival (OS) with chemo-hormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mHSPC): an ECOG-led phase 3 randomized trial. J Clin Oncol. 2014; 32:5s (suppl; abstr LBA2).

5. Bavarian Nordic Initiates Pivotal Phase 3 Trial of PROSTVAC® Prostate Cancer Immunotherapy. http://ci.bavarian-nordic.com/media/news.aspx?news=1919

6. Simpson RJ, Lim JW, Moritz RL, Mathivanan S. Exosomes: proteomic insights and diagnostic potential. Expert Rev Proteomics. 2009 Jun; 6(3): 267-83.

7. Giusti I, Dolo V. Extracellular vesicles in prostate cancer: new future clinical strategies? Biomed Res Int. 2014; 2014: 561571.

8. Yi-Tsung Lu, et al., Current status of liquid biopsies for the detection and management of prostate cancer. Cancer Manag Res. 2019; 11: 5271–5291.

Chapter 15. mCRPC, Genetics and Precision Medicine

1. Marckini R. Brotherhood of the Balloon. http://www.protonbob.com/proton-treatment-homepage.asp.

2. Pedro Isaacsson Velho, et al., Wnt-pathway activating mutations are associated with resistance to first-line abiraterone and enzalutamide in castration-resistant prostate cancer. European Urology, June 2019.

Chapter 19. Complementary Therapies

1. Lee MS, Ernst E. Systematic reviews of t'ai chi: an overview. Br J Sports Med. Aug 2012 46(10): 713-8.

2. Madsen MV, Gøtzsche PC, Hróbjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009 Jan 27; 338: a3115.

3. Jonas WB, Gaddipati JP, Rajeshkumar NV, et al., Can homeopathic treatment slow prostate cancer growth? Integr Cancer Ther. 2006 Dec; 5(4):343-9.

4. Shark Cartilage. American Cancer Society.
http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalte
cartilage

5. Adlerova L, Bartoskova A, Faldyna M. Lactoferrin: a review. Veterinarni Medicina, 53, 2008(9): 457–468.

6. Gibbons JA, Kanwar RK, Kanwar JR. Lactoferrin and cancer in different cancer models. Front Biosci (Schol Ed). 2011 Jun 1; 3:1080-8.

Chapter 20. Diet and Nutrition

1. Vasconcelos A, Santos T, Ravasco P, Neves PM. Dairy Products: Is There an Impact on Promotion of Prostate Cancer? A Review of the Literature. Front Nutr. 2019 May 14; 6:62. doi: 10.3389/fnut.2019.00062.

2. Macdonald R, Tacklind JW, Rutks I, Wilt TJ. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. BJU Int. Vol. 109, Issue 12, pages 1756–1761, June 2012.

3. Khana N, Adhamia VM, Mukhtara HV. Review: Green Tea Polyphenols in Chemoprevention of Prostate Cancer: Preclinical and Clinical Studies. Nutrition and Cancer, Volume 61, Issue 6, 2009.

4. von Holtz RL, Fink CS, Awad AB. beta-Sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. Nutr Cancer. 1998; 32(1): 8-12.

5. Awad AB, Burr AT, Fink CS. Effect of resveratrol and beta-sitosterol in combination on reactive oxygen species and prostaglandin release by PC-3 cells. Prostaglandins Leukot Essent Fatty Acids 72 (3): 219-26, 2005.

6. Obermüller-Jevic UC, Olano-Martin E, Corbacho AM, et al., Lycopene

inhibits the growth of normal human prostate epithelial cells in vitro. J Nutr. 2003 Nov; 133(11): 3356-60.

7. Zhang X-K. Vitamin A and apoptosis in prostate cancer. Endocrine-Related Cancer (2002) 9 87–102.

8. Gaziano JM, Sesso HD, Christen WG, et al., Multivitamins in the prevention of cancer in men: The Physicians' Health Study II randomized controlled trial. JAMA. 2012 Nov 14; 308(18): 1871-80.

9. Ho E. Zinc and Antioxidants in Cancer Chemoprevention. Linus Pauling Institute, Oregon State University. http://lpi.oregonstate.edu/CCP/zinc-cancer.html.

10. Richman EL, Kenfield SA, Chavarro JE, et al., Men With Prostate Cancer Should Eat Healthy Vegetable Fats. UC San Francisco. JAMA Internal Medicine on line 10 June 2013.

11. Richman EL, Kenfield SA, Chavarro JE, et al., Fat Intake After Diagnosis and Risk of Lethal Prostate Cancer and All-Cause Mortality. JAMA Intern Med. 2013; 173(14): 1318-1326.

12. Stacewicz-Sapuntzakis M, Borthakur G, Burns JL, Bowen PE. Correlations of dietary patterns with prostate health. Mol Nutr Food Res. 2008 Jan; 52(1): 114-30.

13. Itsiopoulos C, Hodge A, Kaimakamis, M. Can the Mediterranean diet prevent prostate cancer? Mol Nutr Food Res. 2009 Feb; 53(2):227-39.

14. Sonoda T, Nagata Y, Mori M, et al., A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci. 2004 Mar; 95(3): 238-42.

15. Mori M, Masumori N, Fukuta F, et al., Traditional Japanese diet and prostate cancer. Mol Nutr Food Res. 2009 Feb; 53(2):191-200.

16. Pantuck AJ, Leppert JT, Zomorodian N, et al., Phase II Study of Pomegranate Juice for Men with Rising PSA following Surgery or Radiation for Prostate Cancer. Clinical Cancer Research (Vol. 12 p 4018-4026) 2006.

Chapter 22. Future Developments

1. Costello LC, Franklin RB. A Proposed Efficacious Treatment with Clioquinol (Zinc Ionophore) and Cabergoline (Prolactin Dopamine Agonist) for the Treatment of Terminal Androgen-independent Prostate Cancer. Why and How? https://www.ncbi.nlm.nih.gov/pubmed/30828702

2. Costello LC. The Suppression of Prolactin is required for the Treatment of Advanced Prostate Cancer. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6641560/

Chapter 23. The Role of Support Groups

1. Marckini R. Brotherhood of the Balloon. http://www.protonbob.com/proton-treatment-homepage.asp.

Chapter 29. Enter the Case for Hyperthermia

1. Douwes FR, Lieberman S., Radio-frequency Transurethral Hyperthermia and Complete Androgen Blockade. Jnl of Alternative & Complementary Therapies 7:6: 291-295, 2001.

Appendix 5.

Proton Beam Centres

Proton Beam Therapy is regarded by sections of the medical fraternity as an experimental technique with outcomes not fully confirmed by long term randomized controlled studies. PBT is the most advanced radiation therapy technique available today and continues to rapidly progress from a technological standpoint. The relatively small number of centres world-wide, also contribute to general ignorance of the technique amongst general practitioners and even urologists and radiation oncologists in almost every country. This Star Wars-like technology has been used in the treatment of malignant and benign tumours since the 1950′s. As of 2011, over 73,000 patients have been treated at proton beam treatment centres around the world. By mid-2019 this number will have grown to more than 140,000 patients. The number of these centres is growing quickly with around 63 presently treating patients for prostate cancer and another 12 likely to start treating patients before 2022.

There are a small number of Proton Beam Centres around the world that are fixed beam systems that only treat cancers of the eye or the head or neck. These facilities are omitted from the listing below.

For more details on the individual proton beam centres, go to http://www.anabcofprostatecancer.com.au.

Presently Treating Prostate Cancer Patients - USA

James M. Slater, M.D. Proton Treatment and Research Centre, Loma Linda University Medical Centre, California

The University of Florida Proton Therapy Institute, Florida

M.D. Anderson Cancer Centre’s Proton Centre, Houston, Texas

ProCure Proton Therapy Centre, Oklahoma City, Oklahoma

The Roberts Proton Therapy Centre, University of PA Health System, Philadelphia

Hampton University Proton Therapy Institute, Virginia

CDH Proton Centre, Chicago Area, Illinois

Francis H. Burr Proton Centre, Boston, Massachusetts

NJ/Metro New York ProCure Proton Therapy Centre, New Jersey

ProCure SCCA Proton Therapy Centre, Seattle, Washington

The Provision Proton Therapy Centre, Knoxville, Tennessee

Barnes Jewish Hospital, St. Louis, Missouri

The Scripps Proton Therapy Centre, San Diego, California

Willis-Knighton Proton Therapy Centre, Shreveport, Louisiana

UF Health Cancer Centre at Orlando Health Proton Therapy Centre, Orlando, Florida

Mayo Clinic Proton Beam Therapy Centre, Rochester, Minnesota

Mayo Clinic Proton Beam Therapy Centre, Phoenix, Arizona

Robert Wood Johnson University Hospital, New Jersey

Ackerman Cancer Centre, Jacksonville, Florida

Maryland Proton Treatment Centre, Baltimore, Maryland

Texas Proton Therapy Centre LLC, Irving, Texas

University Hospitals, Seidman Cancer Centre, Cleveland, Ohio

The McLaren Proton Therapy Centre, Flint, Michigan

Proton Therapy Centre, Beaumont Hospital Cancer Institute, Royal Oak, Missouri

Georgetown Lombardi Comp. Cancer Centre, Washington D.C.

New York Proton Centre, New York, NY.

USA – Under Construction or Development - Opening after August 2019

The Stephenson Cancer Centre, Oklahoma City, Oklahoma

The Emory Proton Therapy Centre, Atlanta, Georgia

Dallas Proton Treatment Centre, Dallas, Texas

Johns Hopkins Sibley Hosp. Proton Therapy Centre, Washington, DC

Los Angeles Proton Therapy Centre, Montebello, California

Scott Hamilton Proton Therapy Centre, Franklin, Tennessee

University of Alabama, Birmingham, Alabama

Delray Radiation Therapy Centre, Delray Beach, Florida

Providence Proton, St. Vincent's Hospital, Birmingham, Alabama

Inova Schar Cancer Institute, Fairfax, Virginia

The University of Kansas Health System, Kansas City, Kansas

Mayo Clinic, Jacksonville, Florida.

USA - Planned Facilities

There are other proton beam centres in the USA in the planning stage. The first commercial proton therapy centre at Loma Linda recently treated its 16,000th patient. The technique has clearly fully become of age.

Other Countries – Now Treating Patients

Wanjie Proton Therapy Centre, Zibo, China

Proton Therapy Centre s.r.o., Prague, Czech Republic

Centre Antoine-Lacassagne (CAL), Nice, France

Centre de Protontherapie de I’Instit Curie, Paris, France

West German Proton Therapy Centre, Essen, WPE, Germany

Rinecker Proton Therapy Centre, Munich, Germany

University Hospital Carl Gustav Carus, Dresden, Germany

Heidelberg Ion-Beam Therapy Centre (HIT), Heidelberg, Germany

ATrep – Agenziav Provinciale per la Protontherapia, Trento TN, Italy

The National Cancer Centre, Kashiwa, Japan

Fukui Prefectural Hospital, Fukui City, Japan

Shizuoka Cancer Centre, Shizuoka, Japan

Nagoya Proton Therapy Centre, Nagoya, Japan

Medipolis Medical Research Institute, Japan

Southern Tohuko Proton Therapy Centre, Fukushima, Japan

Proton Medical Research Centre (PMRC), University of Tsukuba, Ibaraki, Japan

Okayama University/Tsuyama Chuo Hospital Proton Beam Cancer Centre, Southern Japan

Federal High-Technology Centre of Nuclear Medicine of FMBA, Dimitrovgrad, Russia

Skandion Clinic, Uppsala, Sweden

The Proton Therapy Centre, National Cancer Centre, Ilsandong, South Korea

Paul Scherrer Institut, Villigen, Switzerland

Chang Gung Memorial Hospital, Taipei, Taiwan.

Appendix 6.

Acknowledgements

I would like to thank my wife for giving me enormous support during my prostate cancer journey. Also, I thank her for her patience in my ‘absence in my study’ for hundreds and hundreds of hours, whilst I researched and wrote this book, the 2nd edition and their predecessor, “An ABC of Prostate Cancer in 2015.” I am sure she became very tired of my singular focus on completing the ‘project’.

My late brother, Brian, gave me a generous insight into his treatment. As an accomplished author of over 50 eBooks which featured his travels through many lands over three decades, he gave me many valuable tips on getting this book published.

My main proof readers, Russell and Geoffrey did an excellent job. Russell’s focus was on English grammar, whilst Geoffrey focussed on the technology, particularly in the diagnostics and genetics areas.

My good friend John is thanked for introducing me to proton beam therapy and other prostate cancer sufferers that had different prostate cancer treatments, with differing outcomes.

I must thank the busy members of the medical profession, who committed their valuable time to read the manuscript and to offer me suggestions for its

improvement. It is appropriate to thank my doctors in Australia and at the NCC in Korea for their professional care and attention during my illness.

Thanks also to ‘Rob’ for sharing his story with us in the last chapter of the book. He also gave interesting input after reading the first edition of the book.

I hope that I have not overlooked anyone. For more information go to www.anabcofprostatecancer.com.au.